UTMJ

University of Toronto Medical Journal

Volume 78, Number 1/December, 2000

A student-run scientific publication. Established in 1923.

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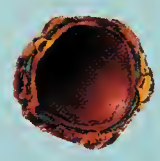

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‡ Results at 16 weeks in a study of 305 hypercholesterolemic patients taking LIPITOR 10 mg or Pravachol 20 mg in a one-year, randomized, double-blind study. The LIPITOR group had LDL-C and TC reductions of 35% and 25% and an HDL-C increase of 6%, while the Pravachol group had LDL-C and TC reductions of 23% and 17% respectively ($p<0.05$) and an HDL-C increase of 8%.

LIPITOR* is an HMG-CoA reductase inhibitor (statin). LIPITOR is indicated as an adjunct to diet for the reduction of elevated total cholesterol, LDL-C, triglycerides, and apolipoprotein B in hyperlipidemic and dyslipidemic conditions (including primary hypercholesterolemia, combined [mixed] hyperlipidemia, dysbetalipoproteinemia, hypertriglyceridemia, and familial hypercholesterolemia) when response to diet and other non-pharmacological measures alone has been inadequate. See prescribing information for complete warnings, precautions, dosing and administration. LIPITOR is contraindicated during pregnancy and lactation. Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines. Caution should be exercised in severely hypercholesterolemic patients who are also renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors. Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently. The effects of [illegible] on cardiovascular morbidity and mortality have not been established.

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A Letter to Our Patrons

We would like to take this opportunity to thank you for your continuing patronage of the *University of Toronto Medical Journal*. We appreciate your continued commitment to the journal and we know that you are central in maintaining the proud tradition of the oldest student-run medical journal in Canada. Indeed, many of the individuals who are currently patrons of the *UTMJ* have been so for years. We are indebted to you for your continued support. We are also grateful to the members of our faculty editorial board, who are essential in maintaining the standard of excellence found in our original papers and review articles. In addition, our faculty advisory board, headed by Dr. Allan Detsky, has provided us with much support and has played an increasingly important role in establishing the *UTMJ* as a premiere journal within and outside our university. As the final volume of the 77th year of publication came to a close earlier this year, we were struck by the increasing level of excellence displayed by the *UTMJ*. The issues of the 77th volume of the journal are of surpassing quality; the continually increasing standards have helped make the *UTMJ* a highly professional and respectable medical journal.

Our goals for the *journal* in 2000-2001 include:

- Maintaining the high standards that you have come to expect of the *UTMJ*.
- Providing all medical students with an arena in which to showcase their work, as well as providing a forum to keep students abreast of recent medical advances and expose them to the diverse facets of clinical medicine and medical research.
- Providing useful resources, including interesting medical pathologies, novel medical technologies, and reviews of important discoveries for clinicians, residents and researchers alike to be used as a tool for review and a vehicle for education.
- To provide an overview of ongoing research at the University of Toronto, to facilitate and encourage collaboration among the research community and further establish the importance of the University of Toronto in the international scientific community.

In this 78th year of publication, we continue to involve a large student-run editorial board which is committed to upholding the excellence of the journal, and hope to establish it as an essential journal showcasing medical and scientific talent at U of T and throughout the world. To that end, we have chosen to introduce a new section: Historical Review. This series aims to publicize important discoveries made at our university. We have also expanded our Clinicopathology section to focus on two very different and unique medical cases. We will also continue to profile both currently and historically important biomedical investigators, whose successes have contributed to the worldwide recognition associated with the University of Toronto. An expansion and improvement of the *UTMJ* website (www.utmj.org) is also underway, in keeping with the increasing role of online journals and resources in biomedical research, and to improve access to past issues. As patrons, you will soon be able to peruse current issues of the *UTMJ* online using a personal password. We will also be offering the $1000 *UTMJ* Editors' Award for the second year to encourage high calibre submissions. This award will be presented to the most deserving submission of the 78th volume. Lastly, we will continue to make the journal accessible to individuals at all levels within the medical profession, so that it may serve as a resource to all.

In closing, we hope that you have found the *UTMJ* to be a valuable asset in your lifelong pursuits of biomedical research and/or practice, and trust that we may rely upon your continued support of our endeavours to make each new issue of the journal better than the last.

Please help us bolster support for the journal by encouraging colleagues and peers to subscribe, and by encouraging personal and student submissions so that we may continue to uphold the proud tradition of this biomedical forum and further establish it as a premiere journal in the world literature.

Prateek Lala and Valerie Panet-Raymond
Editors-in-Chief, 2000-2001

Preface from the Editors

In the first issue of the 78th volume of the *UTMJ*, we aim to examine a wide variety of aspeets in both elinieal medieal and biomedieal research. We hope to represent the dynamie nature of the field of medieine that in a matter of years has progressed from an aneedotal approaeh to an evidenee-based praetiee, and from disease-oriented treatment to patient management that encompasses the many determinants of health. Therapies are no longer limited to underlying pathophysiology, but instead extend inereasingly into the realms of psyehosocial and environmental factors. As we become more aware of the multifaeeted nature of medieal praetice, a multidisciplinary approach to patient eare beeomes more popular and necessary.

We begin this issue with an interesting artiele by Horton *et al.* that examines the trials and tribulations of living with faeial differenees. More speeifieally, the authors consider some of the psyehosoeial faetors and impaets of facial differenees, and propose possible areas of intervention. The next feature artiele takes us from beneh to bedside, as Hajdur and Kalia review the moleeular biology of muscular dystrophies and its clinieal implications. Our third feature artiele delves into the clinieal aspects and theoretieal neurophysiology of the unusual phenomenon known as phantom limb pain.

In this issue, we have deeided to expand one of our most popular seetions, clinicopathologieal correlation (CPC), to two very different and intriguing medieal eases. Lim and Shih take us through the numerous differential diagnoses of a perplexing form of peripheral neuropathy. The steps leading to a diagnosis are presented sequentially and in a manner that is sure to interest everyone from the noviee to the skilled diagnostician. Boggild *et al.* present the case of "the parasite that wasn't," a faseinating look into an unusual but possibly not uneommon phenomenon.

We have also ehosen this opportunity to introduee two new seetions: Historical Review and the *UTMJ* Crossword. Historieal Review aims to step back in time and explore the eontributions that University of Toronto researehers have made to the biomedical seienees. In the first edition of this seetion, Kepron *et al.* examine some of the impressive genetie diseoveries that have been made behind the walls of UofT. The *UTMJ* Crossword is a content-oriented puzzle that uses medieal (and some not-so medical) clues to challenge you; it is eonstrueted with your amusement in mind.

We eontinue to inelude the seetions you have come to expect from the *UTMJ*, sueh as Quiek Diagnosis, whieh eontains short summaries of remarkable patient presentations that ehallenge you, the reader, to formulate diagnoses. The News and Views section ineludes features sueh as: In the Literature, Law and Ethics, and a Forum on the true cost of rising medical sehool tuition fees in Ontario. We also profile this year's winners of the prestigious Gairdner Awards, bestowed upon distinguished medical seientists who have made substantial eontributions to their respeetive fields. We review eaeh winner and their diseoveries, and also present an interview with one of the winners, Dr. Jack Hirsh.

With this first issue, we begin our tenure as editors and look forward to showcasing a variety of innovative articles and cases. We would like to take this opportunity to eongratulate our predeeessors, Raymond Kim and Peter Stotland, on their work in inereasing not only the quality of the journal but its stature as well. It is greatly as a result of their determined efforts that we enjoy an inerease in overall readership and support from our faculty. We will endeavour to maintain their standards of excellence.

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LIPITOR®

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EFFICACY TO REACH TARGET THE FIRST TIME

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THERAPEUTIC CLASSIFICATION Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

LIPITOR (atorvastatin calcium) is a synthetic lipid lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake and catabolism of Low Density Lipoprotein (LDL).

LIPITOR reduces LDL Cholesterol (LDL-C) and the number of LDL particles. LIPITOR also reduces Very Low Density Lipoprotein Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated serum LDL-cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions.

Mean distribution of atorvastatin is approximately 381 litres. Atorvastatin is ≥98% bound to plasma proteins. Atorvastatin is extensively metabolized by cytochrome P-450 3A4 to ortho- and para-hydroxylated derivatives and to various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG Co-A reductase is attributed to active metabolites.

Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer lived active metabolites.

INDICATIONS AND CLINICAL USE

LIPITOR (atorvastatin calcium) is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated total cholesterol, (total-C), LDL-C, TG and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

- Primary hypercholesterolemia (Type IIa),
- Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern;
- Dysbetalipoproteinemia (Type III);
- Hypertriglyceridemia (Type IV),
- Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly to moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25 - 56%) and LDL-C levels (23 - 40%). Chylomicrons, which characterize Types I and V, have not been measured in clinical studies in patients with high TG levels (>11 mmol/L).

In an open label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and IDL-C + VLDL-C levels (34-58%).

In an open label study in patients with homozygous familial hypercholesterolemia (FH), LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients (see PHARMACOLOGY, Clinical Studies).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACOLOGY, Clinical Studies.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

$$\text{LDL-C (mmol/L)} = \text{total-C} - [(0.37 \times \text{(TG)}) + \text{HDL-C})]$$

$$\text{LDL-C (mg/dL)} = \text{total-C} - [(0.2 \times \text{(TG)}) + \text{HDL-C})]^{1}$$

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

The Atorvastatin Versus Revascularization Treatments (AVERT) study examined the effect of intensivre lipid-lowering in patients with stable coronary artery disease and LDL-C at least 3.0 mmol/L in patients referred for percutaneous transluminal coronary angioplasty (PTCA). Patients were randomised for 18 months to LIPITOR 80 mg daily or to PTCA with usual medical care which could include lipid metabolism regulators. The results of the AVERT study should be considered as exploratory since several limitations may affect its design and conduct. In the medical-treated group with LIPITOR there was a trend for a reduced incidence of ischemic events and time to first ischemic event. The results also suggest that intensive treatment to target LDL-C levels with LIPITOR is **additive and complementary** to angioplasty and would benefit patients referred for this procedure (see SELECTED BIBLIOGRAPHY).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme. See WARNINGS, Muscle effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450-mediated interactions.

Hepatic Effects

In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in [illegible]% of patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR; if such a condition should develop during therapy, the drug should be discontinued.

Muscle Effects

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of pharmacokinetic studies conducted in healthy subjects with erythromycin and clarithromycin, thebenefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions). Rhabdomyolysis has been reported in very rare cases with LIPITOR (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been reported with HMG-CoA reductase inhibitors. LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

The effects of atorvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol on cardiovascular morbidity or mortality or total mortality have not been established.

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

Effect on the Lens

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Effect on Ubiquinone (CoQ_{10}) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY).

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) levels. Until further experience is obtained, it is suggested, where feasible, that measurements of serum Lp(a) be followed up in patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY).

Hypersensitivity

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

Use in Pregnancy

LIPITOR is contraindicated during pregnancy (see CONTRAINDICATIONS).

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause harm to the fetus when administered to pregnant women.

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

Nursing Mothers

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Geriatric Use

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see PHARMACOLOGY, Human Pharmacokinetics; SELECTED BIBLIOGRAPHY).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects; PRECAUTIONS, Drug Interactions).

Refer also to DOSAGE AND ADMINISTRATION.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Pharmacokinetic Interaction Studies and Potential Drug Interactions

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see also Geriatric Use; Renal Insufficiency; Patients with Severe Hypercholesterolemia).

Concomitant Therapy with Other Lipid Metabolism Regulators: Combined drug therapy should be approached with caution as information from controlled studies is limited

Bile Acid Sequestrants:

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LOL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to that with LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone.

However, the combination drug therapy was less effective in lowering the triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least two hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid): Although there is no experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration (see WARNINGS, Muscle Effects).

Coumarin Anticoagulants: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTEO BIBLIOGRAPHY).

Digoxin: In healthy subjects, digoxin pharmacokinetics at steady-state were not significantly altered by coadministration of digoxin 0.25 mg and LIPITOR 10 mg daily. However, digoxin steady-state concentrations increased approximately 20% following coadministration of digoxin 0.25 mg and LIPITOR 80 mg daily (see Human Pharmacokinetics). Patients taking digoxin should be monitored appropriately.

Antihypertensive agents (amlodipine): In clinical studies, LIPITOR was used concomitantly with antihypertensive agents without evidence to date of clinically significant adverse interactions. In healthy subjects, atorvastatin pharmacokinetics were not altered by the coadministration of LIPITOR 80 mg and amlodipine 10 mg at steady state (see Human Pharmacokinetics).

Oral Contraceptives and Hormone Replacement Therapy: Coadministration of LIPITOR with an oral contraceptive, containing 1 mg norethindrone and 35µg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive. In clinical studies, LIPITOR was used concomitantly with estrogen replacement therapy without evidence to date of clinically significant adverse interactions.

Antacids: Administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Cimetidine: Administration of cimetidine with LIPITOR did not alter plasma concentrations or LOL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, some macrolide antibiotics (i.e. erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), or the antidepressant, nefazodone, may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY). Caution should thus be exercised with concomitant use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Endocrine Function; OOSAGE ANO ADMINISTRATION; SELECTEO BIBLIOGRAPHY).

In healthy subjects, coadministration of maximum doses of both atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The OTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g. pre-existing prolonged OT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions; OOSAGE AND ADMINISTRATION).

Antipyrine: Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin): In healthy adults, coadministration of LIPITOR (10 mg OO) and azithromycin (500 mg OD) did not significantly alter the plasma concentrations of atorvastatin. However, coadministration of atorvastatin (10 mg OO) with erythromycin (500 mg OIO) or clarithromycin (500 mg BIO), which are both CYP 3A4 inhibitors, increased plasma concentrations of atorvastatin approximately 40% and 80%, respectively (see WARNINGS, Muscle Effects; Human Pharmacokinetics).

Patients with Severe Hypercholesterolemia: Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions; DDSAGE AND ADMINISTRATION).**

Drug/Laboratory Test Interactions

LIPITOR may elevate serum transaminase and CPK levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid-lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

TABLE 1. Associated Adverse Events Reported in ≥1% of Patients in Placebo-Controlled Clinical Trials

	Placebo % (n=270)	LIPITOR % (n=1122)
GASTROINTESTINAL		
Constipation	1	1
Diarrhea	1	1
Dyspepsia	2	1
Flatulence	2	1
Nausea	0	1
NERVOUS SYSTEM		
Headache	2	1
MISCELLANEOUS		
Pain	<1	1
Myalgia	1	1
Asthenia	<1	1

The following additional adverse events were reported in clinical trials; not all events listed below have been associated with a causal relationship to LIPITOR therapy: Muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia

Post-marketing experience: Very rare reports: severe myopathy with or without rhabdomyolysis (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Orug Interactions). Isolated reports: thrombocytopenia, arthralgia and allergic reactions including urticaria, angioneurotic edema, anaphylaxis and bullous rashes (including erytheme multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis). These may have no causal relationship to atorvastatin.

Ophthalmologic observations: see PRECAUTIONS.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required Oue to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the American Heart Association (AHA) Step 1 diet] before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR If appropriate, a program of weight control and physical exercise should be implemented.Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia, Including Familial Combined Hyperlipidemia The recommended dose of LIPITOR is 10 mg once a day. The majority of patients achieve and maintain target cholesterol levels with LIPITOR 10 mg/day. A significant therapeutic response is evident within two weeks, and the maximum response is usually achieved within two to four weeks. The response is maintained during chronic therapy.

Doses can be given at any time of the day, with or without food, and should preferably be given in the evening Doses should be individualized according to baseline LOL-C and/or TG levels, the desired LDL-C and/or TG target (see the Detection and Management of Hypercholesterolemia, Working Group on Hypercholesterolemia and other Oyslipidemias [Canada] and/or the US National Cholesterol Education Program [NCEP]), the goal of therapy and the patient's response. Adjustments of dosage, if necessary, should be made at intervals of four weeks or more. The recommended dose range for most patients is 10 to 40 mg/day. The maximum dose is 80 mg/day, which may be required in a minority of patients (see section below).

Lipid levels should be monitored periodically and, if necessary, the dose of LIPITDR adjusted based on target lipid levels recommended by guidelines.

The following reductions in total cholesterol and LOL-C levels have been observed in two dose-response studies, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia:

TABLE 2. Dose-Response in Patients With Mild to Moderate Hypercholesterolemia
(Mean Percent Change from Baseline)[a]

Lipid Parameter	LIPITOR Dose (mg/day)			
	10 (N=22)	20 (N=20)	40 (N=21)	80 (N=23)
Total-C: 7.1 mmol/L[b] (273 mg/dL)[b]	-29	-33	-37	-45
LDL-C: 4.9 mmol/L[b] (190 mg/dL)[b]	-39	-43	-50	-60

[a]Results are pooled from 2 dose-response studies.
[b]Mean baseline values.

Severe Dyslipidemias:

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Orug Interactions).

Concomitant Therapy

See PRECAUTIONS, Drug Interactions.

Dosage in Patients With Renal Insufficiency

See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance

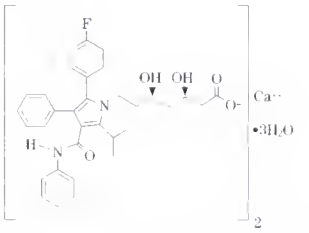
Proper Name: Atorvastatin calcium

Chemical Name: [R-(R*,R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Empirical Formula. $(C_{33}H_{34}FN_2O_5)_2Ca \bullet 3H_2O$

Molecular Weight. 1209.42

Structural Formula:



Oescription: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Tablet Composition:

Each tablet contains either 10 mg, 20 mg or 40 mg atorvastatin as the active ingredient. Each tablet also contains the following non-medicinal ingredients: calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, polysorbate 80 and simethicone emulsion.

Stability and Storage Recommendations:

Store at controlled room temperature 15 to 25°C.

AVAILABILITY OF DDSAGE FDRMS

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg and 40 mg atorvastatin per tablet.

1D mg: White, elliptical, film-coated tablet, coded "10" on one side and "PD 155" on the other. Available in bottles of 90 tablets.

2D mg: White, elliptical, film-coated tablet, coded "20" on one side and "PD 156" on the other Available in bottles of 90 tablets.

40 mg: White, elliptical, film-coated tablet, coded "40" on one side and "PO 157" on the other. Available in bottles of 90 tablets.

References:

1. Koren MJ, Smith DG, Hunninghake OB, *et al*. The cost of reaching National Cholesterol Education Program goals in hypercholesterolemic patients: A comparison of atorvastatin, simvastatin, lovastatin and fluvastatin. *Pharmacoeconomics* 1998;14:59-70. 2. LIPITOR (atorvastatin calcium) Product Monograph, Parke-Oavis Div., Warner-Lambert Canada Inc., June 2000. 3. Oart A, Jerums G, Nicholson G, d'Emden M, Hamilton-Craig I, Tallis G, Best J, West M, Sullivan O, Bracs P, Black O. A multicenter, double-blind, 1-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol* 1997;80:39-44. 4. Bertolini S, Bitollo Bon G, Campbell LM, Farnier M. Langan J, Mahla G, Pauciullo P, Sirtori C, Egros F, Fayyad R, Nawrocki J The efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia *Atherosclerosis* 1997;130:191-197. 5. Data on file. 6. Ontario Orug Benefit Formulary, April 1999.

For a copy of the Product Monograph or full Prescribing Information, please contact.

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Patients with Facial Difference: Assessment of Information and Psychosocial Support Needs

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Abstract

Adults with congenital or acquired facial differences are a defined group of individuals in the community facing unique psychological and social issues. Despite multidisciplinary intervention, many individuals face lifelong challenges, which can adversely affect body image, self-esteem and quality of life. Nonprofit organizations such as *AboutFace* provide information and emotional support to individuals touched by facial differences. A pilot partnership project was proposed to qualitatively investigate the needs of adults with craniofacial deformities at Sunnybrook Health Sciences Centre. Questionnaires exploring epidemiology, issues and concerns, coping strategies and future program suggestions were mailed to 105 patients. Twenty-six patients (25%) responded, and 5 individuals participated in an in-depth focus group. Approximately equal numbers of males and females (mean age 34 years, range 16 to 54 years) with facial differences arising from congenital (46%), post-traumatic, (46%), or post-ablative (8%) means responded. Strategies used by patients to cope with their facial difference differed significantly from current services offered by *AboutFace*. While enthusiastic interest was expressed for the development of information and support programs, it is clear that several nonsurgical needs of patients with facial difference are not currently being met. An alliance between clinical and community programs is proposed to aid in the development of a comprehensive treatment plan for patients with facial differences.

Introduction

Facial Difference

In a society that encourages conformity to an idealized standard of beauty, individuals with facial disfigurements or 'facial difference', are a defined group of individuals who may experience psychological difficulties and social stigma as a result of their appearance.[1] In Canada, approximately 10,000 babies are born with a facial difference annually, while 52,000 individuals acquire a new facial difference each year as the result of injury, disease or illness.[2] People with facial difference, whether present at birth, or due to illness or trauma, may suffer poor body image or self-esteem, creating barriers to friendship, education and employment opportunities.[3]

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Living with a facial difference can impact negatively on self-image and self-esteem, concomitantly affecting psychosocial functioning and quality of life.[4] Self-esteem, considered to be the sum of a person's feelings about him/herself,[5] has been found to be more important in determining social functioning than the degree of deformity itself in facial disfigurements.[6] According to developmental self-theorists, self-perception corresponds to the way in which an individual is perceived by others and how individuals cope with social experiences.[7] A positive self-concept is developed in the setting of regular positive feedback about appearance, while negative feedback from a facial difference can result in a self-fulfilling prophecy,[9] as an individual incorporates perceived negative views of others into his or her self-concept and behaviour.[8,9]

Children born with craniofacial disorders have been found to be more introverted and to express a poorer self-concept more often than children without facial difference,[10] while minor malocclusion is associated with unfavourable self-esteem among young adults.[11] Negative social responses to looking different and reinforcement of these responses in social settings can negatively influence the development of social identity and self-concept.[8] A recent study investigating the psychological functioning of twenty-four adult patients born with a craniofacial anomaly used four different psychological questionnaires to evaluate body image dissatisfaction, self-esteem and quality of life.[12] When compared with a group of non-disfigured, age-matched adults, craniofacial patients reported greater dissatisfaction with their facial appearance, more negative ratings of attractiveness and lower self-esteem. Over a third reported discrimination in social and employment settings because of their facial appearance.

Multidisciplinary Treatment of Facial Difference

The goal of treatment of facial difference by multidisciplinary teams is to improve functional and cosmetic needs while fostering psychological adjustment, positive self-esteem, and healthy interpersonal skills.[13] While reconstructive surgery aims to improve physiologic function and satisfaction with appearance, complete restoration of a disfigurement is rare.[14] Physicians who operate on patients with facial difference are increasingly recognizing the importance of support in treating the 'whole patient': "It is becoming clear…that surgery alone is not sufficient; such patients also require informed supportive counseling…such intervention should not be an optional extra but an integral part of quality care and rehabilitation".[1] As a complement to the vital role of surgery in addressing facial difference, it is equally important to recognize the

importance of support from family and friends, social skills and the prevailing beliefs of society.[3] Having a strong social support network may facilitate the process of adjustment and coping with facial difference.[15]

Community supports for patients with facial differences include *AboutFace*,[2] a Toronto-based nonprofit organization where objectives include providing information on issues related to facial difference, networking individuals for information sharing and emotional support and educating the public about the abilities and challenges in facial difference. Other regional agencies addressing issues related to facial difference include *Changing Faces* (London, England),[16] *Smiles* (USA),[17] *Let's Face It* (Washington),[18] and *The Disfigurement Guidance Centre*.[19]

A pilot partnership project was proposed in order to explore the potential for an alliance between *AboutFace* and the Craniofacial Program at the Sunnybrook Health Science Centre (SHSC). Objectives of the project were (1) to investigate the needs of adults with craniofacial disorders, (2) to establish a link between *AboutFace* and the SHSC Craniofacial Program, (3) to help plan for services which best meet the identified needs of adults with facial differences, and (4) to make recommendations for the initiation of future *AboutFace*-community partnerships.

Method

Patients with facial differences treated by a single craniofacial surgeon at Sunnybrook Health Science Centre, a Level I trauma unit, served as the study population. All participants were adults with congenital or acquired facial differences. Patients with significant cognitive dysfunction were excluded. A four-page questionnaire was used to qualitatively investigate epidemiology (age, sex, cause and duration of facial difference), coping strategies and suggestions for future support programs. Five-point visual analogue scales were used to semi-quantitatively assess attitudes about self, and issues and concerns related to facial difference. Questions for evaluation were based on data obtained from literature review and agency experience of significant issues expressed by individuals with facial difference. Approval from the SHSC Research Ethics Board was obtained for this study. One hundred and five questionnaires were mailed to patients treated between 1996 and 1998. Data was collected and entered into the FileMaker Pro 3.0 Program for Macintosh. Written responses were recorded as they appeared on the questionnaire. Numerical scores of respondents were averaged and presented as the mean.

A two-hour focus group was conducted at SHSC and facilitated by two of the authors (KMH, LR) in order to gain additional insight into the unique issues and needs of adults with facial difference. A consent form acknowledging and accepting audiotaping of the session was signed by participants at the beginning of the focus group, for the purpose of recall and summary of the discussion. Participants were encouraged to speak freely and share their thoughts and ideas in a non-threatening, comfortable environment.

Results

Questionnaire Response

Of 105 questionnaires, 26 were completed and returned, yielding a 25% response rate (summarized in Table I). Another 31 packages were returned unopened due to a change in address, and the remaining 48 were unaccounted for. The respondents included 12 males and 14 females. Respondent age ranged from 16 to 54 years with a mean age of 34 years. Cause of facial difference was categorized as congenital, post-traumatic or post-ablative. Twelve patients each had a congenital (46%) or traumatic (46%) cause of their facial difference, while two patients (8%) had ablation of a malignancy (Table I). The average duration of acquired facial difference was 3 years (range 2.0 - 6.5 years).

Of the 26 respondents, none had personal involvement with *AboutFace*, but 23% were aware of the organization's existence. Ninety percent (23 participants) indicated interest in future involvement with support organizations. Fifty-four percent (14 participants) were interested in further involvement in the study (focus group), and 5 were able to participate in the focus group.

Table 1
Questionnaire Response

Response rate		25% (26 / 105 questionnaires)	
Males : Females		1.0 : 1.2	
Mean age		34 years	
Age range		19%	16-24 years
		15%	25-34 years
		38%	35-44 years
		27%	45-54 years
Classification	Congenital	12 patients	(46%)
	Post-traumatic	12 patients	(46%)
	Post-ablative	2 patients	(8%)

Surgical Experience

Patients were asked "What helped or would have helped you to prepare for your surgery?". Strategies included preoperative explanations by the physician, the opportunity to ask questions, support from family and friends, counseling, and religion. One patient stated: "I never had any [preparation] throughout my childhood - it was a total nightmare". This experience was echoed among other respondents who had undergone multiple surgeries during childhood, revealing that surgeries were "not asked for, not understood, and explanations were not adequately given". When asked about recovery and needs after surgery, typical responses included emotional support, reassurance, rest and time. Many patients described surprise and frustration at the length of time taken to recover following surgery.

Emotional, social and work-related effects of surgery varied. Some individuals reported improved self-esteem and more self-confidence following surgery, enabling them to lead a more normal life: "I was able to attend school, church, Brownies and Girl Guides". However, other individuals expressed that although they were satisfied with the results of their surgery, their facial difference still affected their life in terms of self-concept, socially or professionally: "Sometimes when I look in the mirror, it's hard to see myself"; "There are still people staring at me and making mean comments"; "I still can't find permanent employment in a public field".

When asked: "What would you say to someone dealing with facial difference for the first time?" and "What did you learn from your experience?", responses included: "I learned how cruel people can be to people with deformities and how ignorant they are of their

"Work on your strengths inside, try to keep a positive attitude, find a surgeon you trust and tell him/her what you want and make them answer your questions!"; "Surgery may not change your life, like you think it might"; and "Society still expects beauty comes from outside - they will not take the time to know you from within".

Attitudes About Self

A five-point visual analogue scale was used to assess participants' attitudes about themselves. Categories included (1) *feelings of attractiveness* (overall, facial, sexual), (2) *social skills* (handling new situations, meeting new people, letting people know me, feelings of belonging), and (3) *self-esteem* (feeling good about myself, confidence in abilities, recognizing my strengths, giving myself credit). Twenty-six scores were averaged, and the mean score was plotted on a scale from 0 to 4 (poor to excellent). A score of 2 was considered average (Figure 1). Respondents scored slightly below average in feelings of attractiveness, average in social skills and scores varied in self-esteem.

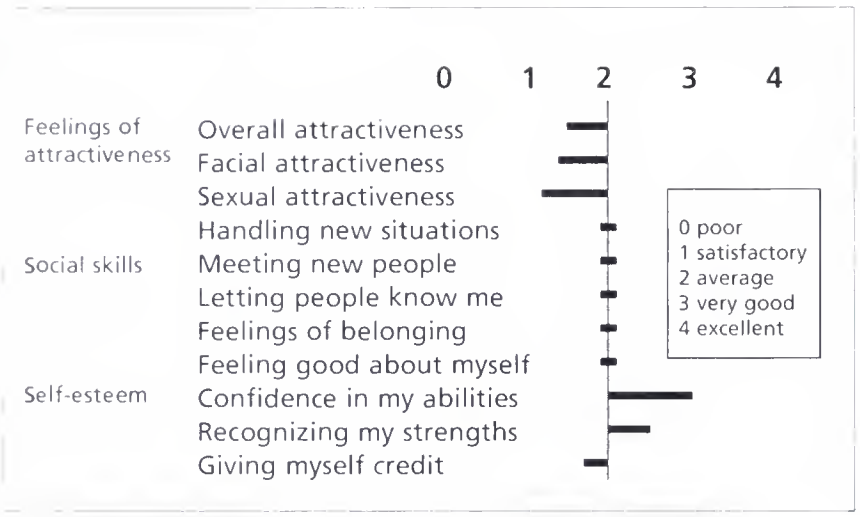

Figure 1. *Attitudes of patients with facial difference (n=26)*

Issues and Concerns

A five-point visual analogue scale was used to assess issues and concerns with respect to self-concept, body image, social and professional situations (Figure 2). High scores ('frequently' or 'always' difficult) were common in interacting with new people, dating or socializing, self-consciousness with appearance, and looking at myself in photos or in the mirror. However, overall numerical trends for issues and concerns related to facial difference were not striking. Individual responses accompanying the numerical scores included forthright statements such as: "People still stare at me all the time"; "I'm tired of doctors saying 'You're in your forties, have a family and work - so what's the problem? Accept yourself!"; and "People still look for physical perfection, especially employers. You learn the hard way to hide your feelings".

Coping Strategies and Program Suggestions

The vast majority of respondents reported that past strategies used to cope with facial difference consisted of talking with family and friends, pursuing hobbies and educating themselves (Figure 3). Fewer patients talked to their physician, avoided social contact or sought counseling as means of coping. A smaller percentage used alcohol or drugs or pursued employment with minimal face-to-face contact. Of special interest was that the most infrequent coping strategies included talking with other adults with a facial difference and attending support groups.

Patients were asked about interest in future services related to facial difference. Significant interest was expressed for information and resources about facial differences, networking with other adults with a facial difference, information sessions (guest speakers, video nights, workshops), syndrome-specific information, and support group meetings (Table 2).

Figure 2. *Issues and concerns of patients with facial difference (n=26)*

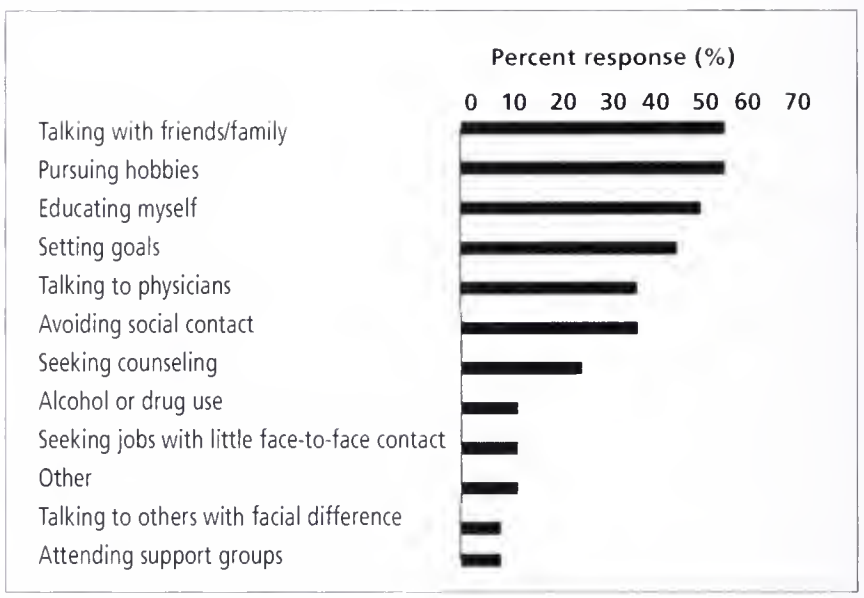

Figure 3. *Coping strategies in facial difference (n=26)*

Focus Group Discussion

A focus group with 5 of the 26 study participants enabled further exploration and elaboration of answers from the questionnaire (results not shown). For many participants, it was the first time they had spoken with other adults with facial difference, or shared their story with anyone outside of their family. One participant with a congenital syndrome, admitted to knowing little about the condition, and had never spoken to another person with the syndrome. Significant enthusiasm was demonstrated for the establishment of informational materials about facial difference and specific congenital syndromes at SHSC. Unequivocal interest was expressed for the establishment of a monthly support group in the community.

Table 2
Support and Information Needs Suggested by Participants (n=26)

Information and resources about facial differences	54%
Networking with other adults with a facial difference	46%
Information sessions (speakers, videos, workshops)	46%
Syndrome-specific information	38%
Support groups or meetings	35%

Discussion

Although reconstructive surgical techniques have made extraordinary advancements in the surgical management of facial differences, inherent psychosocial issues of living and coping with a disfigured face are not always addressed.[1,2] The aim of this project was to qualitatively investigate the information and support needs of adult patients with facial difference at SHSC, and to help plan for community services which best meet these needs.

Over one third of respondents were in the 35 to 44 year age range. It is interesting that many telephone callers to *AboutFace* and organization members themselves are in this age range,[2] indicating the similarity between this subset of the study population and individuals in the community with facial difference who currently seek support services. Furthermore, the wide range of participant ages illustrates that having a facial difference can have an impact at any age, with issues and challenges remaining significant throughout the decades.

It is clear that many adults with facial difference are not aware of organizations such as *AboutFace*, and only a minority of those who are aware of their existence take advantage of their services. From the interest shown in this study, the lack of awareness is likely a consequence of inadequate access to information, rather than disinterest. Perhaps by targeting individuals with newly acquired facial difference directly at trauma centres and introducing support services early, utilization of community resources would be more effective.

The majority of past coping strategies reported by respondents were largely activities that did not involve community programs and which could be achieved independently. Strategies used most infrequently included talking with other adults with a facial difference and attending support groups and services offered by community agencies. This is in contrast to the respondents' significant interest in information and support services.

Results obtained from the focus group confirmed the findings of the questionnaire, namely that despite minimal previous use of information and support resources, many patients with facial difference have a strong interest in the services of a support group. Such a link would directly provide patients with access to these services, with the opportunity to take advantage of these programs, support themselves and facilitate self-education about facial difference.

The diverse attitudes toward surgical outcome and issues related to facial difference imply that although reconstructive surgery aims to improve physiologic function and satisfaction with appearance, many people still experience difficulties in their life not directly addressed by surgery. In order for tertiary care centres to best care for post-surgical patients, it is important for the individual undergoing craniofacial surgery, as well as their family members, friends, and health care professionals to recognize, anticipate and understand these needs. By doing so, an effective support network can be built for the patient, both at treatment centres and in the community.

The results of this study suggest that many of the nonsurgical needs of patients with facial difference are not currently being met. These needs include access to information about their condition, access to general resources related to having a facial difference, and support programs. To date, the clinical focus in facial difference has often been on surgical treatment and ancillary services to address functional difficulties.[1] Organizations founded specifically to support individuals touched by facial difference, provide programs and services that specifically address these issues, such as networking, education, support and outreach in the community.

Direct outcomes of this study have included the initiation of communication between the SHSC Craniofacial Program team and *AboutFace*, and the establishment of a monthly support group for people with facial difference. Future plans include regional distribution of informational materials and organization of educational evenings and workshops.

Initiation of further alliances between tertiary care centres specializing in craniofacial differences and community support agencies will be strongly advantageous in developing a comprehensive treatment plan for these patients. Individuals with facial difference will be encouraged to build supportive networks, participate in their communities and become more self-sufficient through awareness, knowledge and self-realization. Physicians, nurses and other health care providers may develop heightened awareness and a greater understanding of their needs, to better care for patients with facial differences.

Acknowledgements

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References

1. McGrouther DA. (1997). Facial disfigurement: The last bastion of discrimination. *BMJ.* 314:991.
2. AboutFace. (1997). AboutFace background information. AboutFace International Office, 99 Crowns Lane, 4th Floor, Toronto, Ontario, M5R 3P4.
3. Partridge J and Cooper C. (1996). Facial disfigurement - the full picture. A comprehensive guide to facial disfigurement. London, Changing Faces, 1-2 Junction Mews, London, England, W2 1PN.
4. MacGregor FC. (1990) Facial disfigurement: Problems and management of social interaction and implications for mental health. *Aesth Plast Surg.* 14: 249-257.
5. Patzer GL. (1995). Practice made perfect. Self-esteem and physical attractiveness. *J Aesth Dent.* 7:37.
6. Thomas PT, Turner SR, Rumsey N, et al. (1997). Satisfaction with facial appearance among subjects affected by a cleft. *Cleft Pal Craniofac J.* 34:226-231.
7. Goethals GR and Worchel S. (1981). Adjustment and human relations. Alfred Knopf: New York.
8. Kiyak A. (1992) Psychosocial predictors and sequelae of facial change. *J Can Den Assoc.* 58:459-462.
9. Tobiasen JM and Hiebert JM. (1993). Clefting and psychosocial adjustment. Influence of facial aesthetics. *Clin Plast Surg.* 20:623-631.
10. Pertschuk MJ and Whitaker LA. (1985). Psychosocial adjustment and craniofacial malformation in childhood. *Plast Reconstr Surg.* 75:17-182.
11. Helm S, Kreiborg S, and Solow B. (1985). Psychosocial implications of malocclusion: A 15-year follow-up study in 30-year-old Danes. *Am J Orthodont.* 87:110-118.
12. Sarwer DB, Bartlett SP, Whitaker LA, at al. (1999). Adult psychological functioning of individuals born with craniofacial anomalies. *Plast Reconstr Surg.* 103(2):412-418.
13. Kapp-Simon K. (1991). Meeting the challenge: A social skills training program for adolescents with special needs. University of Chicago Press: Chicago.
14. Pertschuk M. (1990). Reconstructive surgery: Objective change of objective deformity. Cash TF and Pruzinsky T (eds). Body images: Development, deviance, and change. Guilford Press: New York, pp. 237-252.
15. Robinson E, Clarke A and Cooper C. (1996). The psychology of facial disfigurement. A guide for health professionals. Changing Faces: London, England.
16. Changing Faces. (1997). Changing Faces: London, England.
17. Smiles Website. (1997). Available from URL: http://www.cleft.org
18. Let's Face It: Resources for People with Facial Difference. (1997). P.O. Box 29972, Bellingham, WA, USA. 98229. Available from URL: http://www.nas.com/~let's-faceit
19. Centre TDG: The Disfigurement Guidance Centre Website. (1998). Available from URL: http://www.timewarp.demon.co.uk/dgc.html#workshop

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Dystrophinopathies and Nondystrophinopathies: From Molecular Biology to Clinical Diagnosis

Lorraine V. Hajdur, BSc (MD/PhD Program)* and Suneil K. Kalia, BSc (MD/PhD Program)

Abstract

Muscular dystrophies are a heterogeneous group of inherited disorders that are clinically characterized by progressive loss of muscle integrity, muscle wasting and weakness. The heterogeneity of phenotypes and overlap of clinical symptoms among various dystrophies often limit the utility of any classification scheme that is based solely on the clinical features. Identification of dystrophin as the mutated protein in Duchenne muscular dystrophy has led to the classification of muscular dystrophies into two groups: (i) those muscle disorders involving dystrophin (dystrophinopathies); and, (ii) those muscle disorders involving other known dystrophin-associated proteins (DAPs) or as of yet unidentified gene products (nondystrophinopathies). We will describe the molecular biology of dystrophin and DAPs and outline their roles in both physiological and pathological muscle function. This will provide a framework for the discussion of current approaches to the diagnosis of dystrophinopathies and nondystrophinopathies.

Introduction

The muscular dystrophies are a heterogeneous group of inherited disorders that typically involve striated muscle, including both skeletal and cardiac tissue. There is a wide variety of clinical types and variations of muscular dystrophies; however, a unifying feature of the disorders is the histological findings of muscle samples from biopsy which demonstrate variation in fiber size, muscle cell necrosis and regeneration, and often proliferation of adipose and connective tissues. This progressive breakdown of muscle integrity leads to the muscle wasting and weakness that clinically characterize these myogenic disorders; the muscle group(s) involved depends on the form of muscular dystrophy.[1,2]

Traditionally, the muscular dystrophies were classified according to three considerations proposed by Walton and Nattrass in 1954[3]: (i) mode of inheritance; (ii) age of onset; and, (iii) distribution of predominant muscle weakness. However, the heterogeneity of phenotypes and the overlap of clinical symptoms among the dystrophies often limit the utility of a classification scheme based primarily on clinical features. Recently, progress in the genetic and biochemical understanding of muscular dystrophies initiated an evolution in the classification of these disorders (Table 1). Identification of dystrophin as the mutated protein in Duchenne muscular dystrophy (DMD, incidence 30 in 100,000 live born males) has led to an appreciation of a wide range of clinical presentations associated with dystrophin gene mutations. Consequently, muscle disorders involving abnormalities in the protein dystrophin, including DMD and Becker muscular dystrophy (BMD, incidence 3 in 100,000 live born males), are now collectively termed the dystrophinopathies.[2,4] Accordingly, the muscular dystrophies caused by unidentified gene products or other known proteins, such as the sarcoglycans, can be categorized as the nondystrophinopathies. This review focuses on the molecular biology of the muscular dystrophies and will also address some aspects of the clinical features and diagnosis of the dystrophinopathies and nondystrophinopathies. In particular, the main focus of this paper is the muscular dystrophies associated with dystrophin and dystrophin-associated proteins (DAPs) since these disorders constitute some of the most prevalent and best-studied muscular dystrophies.

Molecular Biology of Dystrophin and Dystrophin-Associated Proteins

Progress in understanding the molecular biology of muscular dystrophies has depended on two major approaches: (i) genetic linkage analysis; and, (ii) the candidate gene method. The impetus for research in this field was initiated by the discovery of the gene for the protein dystrophin by Kunkel's group just over a decade ago.[5] Within two years of this finding, biochemical analyses by Campbell and colleagues revealed that dystrophin was associated with a complex of dystrophin-associated proteins (DAPs).[6,7] Currently, research into the DAP complex has revealed that defects in the genes encoding the proteins of this complex cause several different types of muscular dystrophies.[8] Since the present understanding of the pathobiology and diagnosis of the dystrophinopathies and nondystrophinopathies is based on the concept of the DAP complex, current theories regarding the relationship between both the structure and function of this protein complex and the pathogenesis of muscular dystrophies is outlined below.

Structure of the Dystrophin-Associated Protein Complex

The DAP complex is composed of a chain of proteins that traverse the muscle cell membrane, forming a link between the extracellular matrix and intracellular F-actin (Figure 1). This group of proteins can be divided into three domains based on location with respect to the muscle cell membrane: (i) extracellular; (ii) transmembrane; and (iii) intracellular.[9]

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Extracellular Domain

Laminin-2, one of the primary components of the extracellular matrix in striated muscle, is a heterotrimer composed of subunits ß1-laminin, γ1-laminin, and α2-laminin or merosin (90 kDa). Laminin binds at the muscle cell surface to the dystroglycan complex 10 which is composed of two subunits: (i) α–dystroglycan (156 kDa); and, (ii) ß–dystroglycan (43 kDa). The former is a peripheral membrane protein located at the interface between the extracellular matrix and the muscle cell membrane, whereas the latter is thought to be an integral membrane protein that spans the lipid bilayer.[11]

Transmembrane Domain

ß–Dystroglycan binds loosely with the sarcoglycan complex, a complex of at least four tightly associated DAPs. These sarcoglycan glycoproteins include α-, ß-, γ-, and δ-sarcoglycans (50, 43, 35, and 35 kDa, respectively) which are believed to span the muscle cell membrane and interact with proteins within the cytoplasm.[12,13,14,15] Sarcospan, a 25 kDa protein that is predicted to span the sarcolemma, associates with the sarcoglycan complex.[16] Recently, an additional sarcoglycan protein, named ε-sarcoglycan, was cloned based on homology to α-sarcoglycan (adhalin).[17] The function of ε-sarcoglycan in striated muscle is not yet clear, but data suggest that ε-sarcoglycan may replace α-sarcoglycan in the DAP complex of smooth muscle.[18]

Intracellular Domain

Dystrophin (427 kDa) is an enormous, rod-like protein localized to the inner face of the sarcolemma in mature muscle. Due to its large size and parallel orientation to the muscle cell membrane, dystrophin can interact with a number of other membrane-associated proteins. The distal C-terminal region of dystrophin binds to the syntrophin proteins (59 kDa) while the C-terminal cysteine-rich region of dystrophin associates with ß-dystroglycan.[19] In addition, the N-terminal domain of the dystrophin protein can interact with the F-actin filaments of the intracellular cytoskeleton.[20]

Other intracellular DAPs include dystrobrevin which is localized to the subsarcolemma and can associate with both dystrophin and the syntrophins.[21] Caveolin-3, the muscle-specific form of the caveolin protein family, is another intracellular protein that appears to be associated with dystrophin; however, caveolin-3 is not considered to be an integral part of the DAP complex. Located at the sarcolemma, caveolin-3 may act as a scaffolding protein to organize and concentrate specific caveolin-interacting lipids and proteins within caveolae microdomains.[22] Recently, a protein homologous to neuronal nitric oxide synthase (nNOS) has been localized to the intracytoplasmic muscle cell membrane, in close association with dystrophin.[23] Additional proteins are likely be identified as constituents of the DAP complex. For example, vinculin and talin may bind to one or more of the dystrophin-associated proteins.[24,25]

Table 1
Classification of Muscular Dystrophies Based on Molecular Biology

MUSCULAR DYSTROPHY	GENE LOCUS	GENE PRODUCT
Dystrophinopathies		
Duchenne Muscular Dystrophy	Xp21.2	Dystrophin
Becker Muscular Dystrophy	Xp21.2	Dystrophin
NONDYSTROPHINOPATHIES		
Limb-Girdle Muscular Dystrophies (LGMDs)		
Calpainopathy		
LGMD-2A	15q15-21	Calpain-3
Dysferlinopathy		
LGMD-2B	2p13	Dysferlin
Sarcoglycanopathies		
LGMD-2C	13q12	γ-Sarcoglycan
LGMD-2D	17q12-21	α-Sarcoglycan (Adhalin)
LGMD-2E	4q12	ß-Sarcoglycan
LGMD-2F	5q33-34	δ-Sarcoglycan
LGMD-2G	17q11-12	?
LGMD-2H	9q31-34	?
Other LGMDs		
LGMD-1A	5q22-34	?
LGMD-1B	1q11-21	?
LGMD-1C	3p25	Caveolin-3
Congenital Muscular Dystrophies (CMDs)		
CMD I	6q2	α2-Laminin (Merosin)
CMD II (Fukuyama CMD)	9q31	Fukutin
CMD III (Muscle-eye brain disease)	?	?
CMD IV (Walker-Warburg syndrome)	?	?
Emery-Dreifuss Muscular Dystrophy (EDMD)		
X-EDMD	Xq28	Emerin
AD-EDMD	1q21	Lamin A/C
Myotonic Dystrophy	19q13.3	Muscular dystrophy protein kinase (Myotonin)

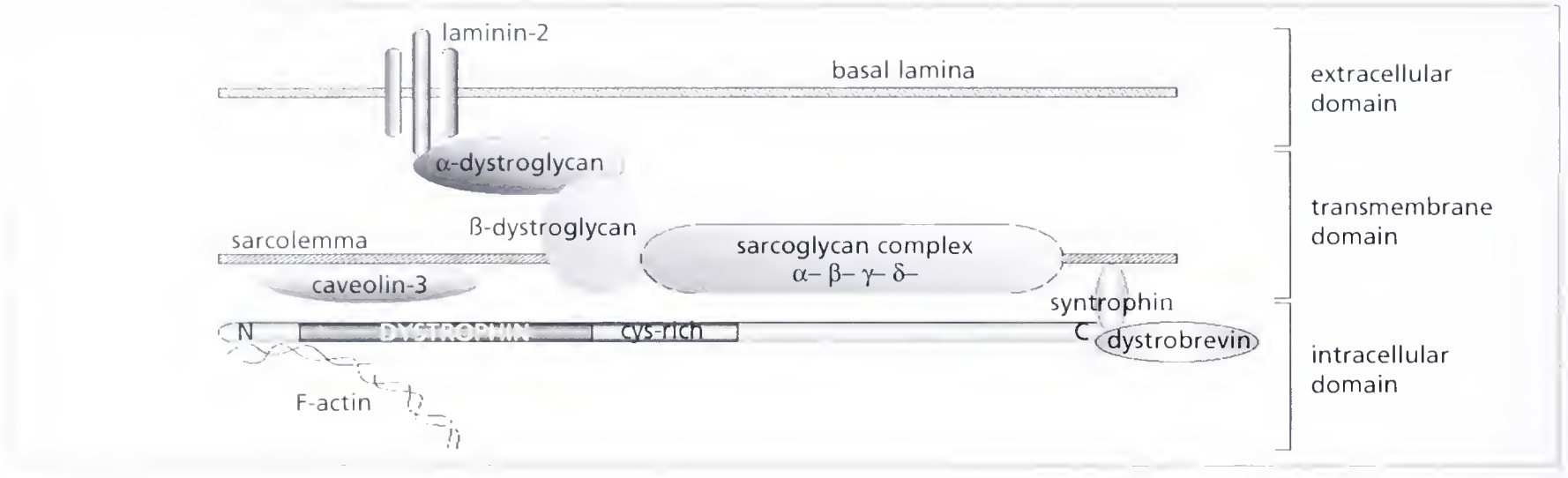


Figure 1. Structure of the Dystrophin-Associated Protein (DAP) Complex

In the extracellular domain, laminin-2 binds to the alpha subunit of dystroglycan at the outer sarcolemmal surface. The beta subunit of dystroglycan is an integral membrane protein that associates with both the sarcoglycan complex and the C-terminal cysteine-rich region of dystrophin. The sarcoglycan complex consists of at least four tightly associated DAPs (α-, ß-, γ-, and δ-sarcoglycans) that constitute the remainder of the transmembrane domain. The key component of the intracellular domain is dystrophin. Dystrophin is localized to the inner face of the sarcolemma and associates with F-actin at its N-terminus, with syntrophin at its C-terminus, and with many other intracellular proteins, including dystrobrevin and caveolin-3.

Function of the Dystrophin-Associated Protein Complex

The functional significance of the extracellular to intracellular protein chain composed of dystrophin and the dystrophin-associated proteins is not known. However, abnormal expression of dystrophin or other components of the DAP complex has been implicated in a variety of different types of muscular dystrophies, as described below. Since dystrophin and the DAPs form a link between the extracellular matrix and the intracellular cytoskeleton, one pathogenic model for these dystrophies suggests that the DAP complex forms a structural bridge which maintains the integrity of the membrane during cycles of contraction and relaxation.[26] Consequently, the absence of any one of these proteins would interfere with membrane integrity and strength, resulting in the muscle weakness associated with muscular dystrophies. However, exactly how the absence of dystrophin or other components of the DAP complex leads to the clinical features of the dystrophinopathies and nondystrophinopathies has not yet been elucidated.[1]

An additional hypothesis suggests that the protein complex may also mediate signalling between the extracellular and intracellular compartments of myocytes. This theory considers the possible functional roles of some of the proteins associated with the DAP complex. For instance, the syntrophins contain a PDZ domain, a well-characterized protein-protein interaction motif that mediates signalling events at both tight junctions and neuronal synapses.[27] Theoretically, the syntrophins may mediate signal transduction at the muscle cell membrane. Similarly, caveolins are proteins thought to play an important role in the formation of caveolae membranes, specialized microdomains of the plasma membrane implicated in a subset of transmembrane signalling events, such as G-protein-coupled signalling.[28] In addition, nNOS has been identified as a signalling molecule in the central nervous system involved in cell death associated with cerebral ischemia.[29] The nNOS homologue associated with the DAP complex may potentially play a role in muscle cell necrosis associated with the muscular dystrophies.

Another pathogenic model for the muscular dystrophies opposes the idea that the DAP complex provides structural integrity to the cell. Instead, this model suggests that dystrophin and DAPs are involved in organizing the membrane cytoskeleton of the myocyte and, in turn, the intracellular cytoskeleton of the muscle cell is responsible for aggregating ion channels and neurotransmitter receptors at the cell membrane.[26] Interestingly, this idea is similar to the emerging role of the cytoskeleton in CNS neurons.[30]

Other Proteins Associated with the Muscular Dystrophies

Basic research in the field of muscular dystrophies has served to emphasize the pivotal role of dystrophin and associated proteins, yet abnormal expression of these proteins alone cannot account for all types of muscular dystrophies. The proteins implicated in many of the other dystrophies have recently been identified and are listed below. How mutations in these proteins are related to the pathogenesis of nondystrophinopathies is not yet known.

Calpain-3, the muscle-specific member of a family of calcium-dependent proteases, appears to exist in both the cytosol and the nucleus of muscle cells[31] and associates with connectin (titin).[32] Unlike the structural proteins contained within the DAP complex, calpain-3 is an enzyme; however, mutations in this regulatory protein can also result in loss of muscle integrity and muscle weakness.[1] Kunkel[33] suggests that defects in calpain-3 seem to be implicated in the dysregulation of regulatory proteolysis in myocytes. The protease may also be involved in regulating muscle cell differentiation by controlling the level of transcription factors within the cell.[31]

Other proteins associated with one or more forms of muscular dystrophy include: dysferlin, the product of a novel mammalian gene that is localized to the muscle fibre membrane;[34] fukutin, a novel protein that is secreted and may be localized to the extracellular matrix[35]; and, the contractile proteins, myosin and tropomyosin.[36,37] Interestingly, proteins associated with the nuclear membrane, such as emerin[38] and lamin A/C,[39] may also be altered in muscular dystrophy. These findings suggest that interactions between nuclear membrane components maintain skeletal and cardiac muscle function and that the loss of integrity of the nuclear envelope is a legitimate cause of muscular dystrophy.[40]

Although research over the past decade has dramatically increased our understanding of this heterogeneous group of diseases, the protein defects associated with several muscular dystrophies have

not yet been identified. For example, facioscapulohumeral dystrophy has been determined to be genetically associated with the distal-most tip of the long arm of chromosome,[4] but this dystrophy has not yet been attributed to defects in a particular gene and gene product.[41] In addition, the genetic defects underlying some of the muscular dystrophies may not simply result in abnormal protein expression. An expanded, noncoding CTG codon repeat at the 3' end of the gene encoding muscular dystrophy protein kinase (myotonin) results in the phenotype of myotonic dystrophy. However, the relationship between the expanded repeat in a noncoding region of the gene and the pathogenesis of myotonic dystrophy has not been thoroughly elucidated.[42,43,44]

Clinical Features of Dystrophinopathies and Nondystrophinopathies

Consistent with the large number of genetic defects and protein abnormalities associated with the muscular dystrophies, this group of muscle disorders is heterogeneous in its clinical presentation. Earlier, diagnosis of the dystrophies required an appreciation of the clinical findings, such as distribution of muscle weakness, and an understanding of the mode of inheritance of these disorders. Today, diagnosing the muscular dystrophies also involves knowledge of the genetics and muscle protein biochemistry. The following section of this review briefly summarizes the clinical features of the major dystrophinopathies and nondystrophinopathies. In addition, the identifications of the loci or genes and the affected proteins that are involved in the pathogenesis of these disorders will be included (also see Table 1).

Dystrophinopathies

Duchenne Muscular Dystrophy and Becker Muscular Dystrophy

Duchenne muscular dystrophy (DMD, incidence 30 in 100,000 live born males) is the most common type of dystrophy, as well as the most frequent muscle disease among children. This dystrophinopathy is clinically characterized by X-linked recessive inheritance, proximal weakness starting in early childhood, pseudohypertrophy of the gastrocnemius muscles, cardiac abnormalities, and up to 10-fold elevations in serum creatine kinase levels. Approximately thirty percent of boys with DMD display some degree of intellectual impairment, suggesting a possible role for dystrophin in normal cognitive development. Progression of the muscle weakness leads to wheelchair dependence by early teens and death from respiratory failure by the end of the third decade of life.[1,2,9,26,45] In the late 1950s, Becker and Walton both noted the existence of an X-linked muscular dystrophy that displayed a later age of onset, as well as a slower rate of progression, than DMD.[46] This newly discovered form of muscular dystrophy was named Becker muscular dystrophy (BMD, incidence 3 in 100,000 live born males). BMD is clinically defined as a slowly progressive dystrophy of late childhood and adult life and the disorder is clinically characterized by muscular weakness affecting the pelvic and shoulder girdles, calf hypertrophy, high serum levels of CK, a myopathic EMG, and a dystrophic muscle biopsy.[47] Unlike DMD patients, most individuals affected by BMD walk well into adult life.[9]

Both DMD and BMD are caused by mutations in the dystrophin gene located on the X chromosome (Xp21.2). This gene is one of the largest gene characterized to date (2.4 Mb) and, consequently, the estimated proportion of spontaneous mutations within the dystrophin gene is high at 0.30.[47] As dystrophinopathies, DMD and BMD both involve mutations in the dystrophin protein, yet their clinical presentations differ. This can be partially explained by the differences in the expression of dystrophin: immunohistochemical analysis of skeletal and cardiac muscle from DMD patients indicate an absence of dystrophin, whereas dystrophin is usually present in muscle, but qualitatively and quantitatively abnormal in people with BMD.[48]

Other Dystrophinopathies

With the discovery of the dystrophin gene and its product, molecular and biochemical assays for identifying dystrophin gene mutations and dystrophin protein abnormalities were developed. This, in turn, led to the identification of other types of dystrophinopathies, as well as to an appreciation of the variability in clinical presentations associated with dystrophin mutations. Currently, the dystrophinopathies include a range of conditions from classic DMD to clinically silent cases of elevated serum CK. In the absence of a muscular dystrophy, dysfunction of other organs can become the predominant clinical feature in these other dystrophinopathies. For example, some patients with X-linked mental retardation and/or psychiatric disorders have been identified with previously unrecognized dystrophin gene mutations. Similarly, a substantial proportion of cases of X-linked dilated cardiomyopathy may result from underlying dystrophin gene defects.[4] Samaha and Quinlan[47] suggest that there may be other dystrophinopathies that are yet to be identified.

Nondystrophinopathies

Limb-Girdle Muscular Dystrophies

The term limb-girdle muscle dystrophy (LGMD) encompasses a diverse set of diseases that affect both males and females. Similar to DMD and BMD, this group of muscular dystrophies presents clinically with weakness and wasting of the limb-girdles, often with elevated serum CK levels.[9] LGMDs are uniformly progressive, but they vary greatly with respect to age of onset and rate of progression.[33] LGMDs were clinically defined by a spectrum ranging from severe weakness with childhood onset to a moderate phenotype in adults and were classified according to their mode of inheritance with the autosomal dominant traits and the autosomal recessive phenotypes named LGMD-1 and LGMD-2, respectively.[49] However, the identification of the dystrophin-associated protein (DAP) complex and the characterization of the complex's role in the pathogenesis of many LGMDs has provided a new basis for the distinction between and classification of these muscular dystrophies (Table 1).

The sarcoglycanopathies are a group of autosomal recessive LGMDs that are characterized by a deficiency in one of the components of the sarcoglycan complex within the DAP complex. Specifically, LGMD-2C, 2D, 2E, and 2F involve defects in γ-, α-, ß-, and δ-sarcoglycan, respectively.[33] Clinical features of the sarcoglycanopathies include calf hypertrophy, involvement of scapular muscle and deltoid in the upper limb at onset of disease, as well as cardiac involvement. The majority of people with a sarcoglycanopathy present in childhood, although onset can occur in adulthood. Progression of the disease ranges from very mild to very severe.[2,9,33,50]

Other LGMDs are not associated with mutations in the sarcoglycan complex. Calpainopathy (LGMD-2A) and dysferlinopathy

LGMD-2B involve mutations in the *CAPN3* gene, which encodes the muscle-specific protein calpain-3, and the dysferlin gene, respectively. Clinically, calf hypertrophy is rarely associated with calpainopathy, but Achilles tendon contractures are common. Muscle involvement in calpainopathy displays an atrophic pattern and may be scapulohumeral at presentation. These patients usually present between the ages of eight and fifteen years, but adult onset is fairly common. Progression of calpainopathy is variable and respiratory complications can be severe. In dysferlinopathy, CK levels are often 20 to 150 times above the normal range at presentation. Other clinical features include predominant proximal or distal lower limb involvement, resulting in early inability to stand on uptoes as a common symptom. Disease onset of dysferlinopathy is usually in the late teens with slow progression of muscle weakness.[20,33,50]

LGMD-1C is an autosomal dominant muscular dystrophy characterized by a caveolin-3 deficiency. The clinical features of the few cases that have been described include calf hypertrophy and muscle pain on exertion. Age of onset is around five years and disease progression is variable.[50]

The remaining LGMDs are only defined by a chromosomal localization since the genes associated with these dystrophies have not yet been cloned. LGMD-2G and 2H are linked to the gene loci 17q11-12 and 9q31-34, respectively.[51,52] The genes for LGMD-1A and 1B have been localized to chromosomes 5q22-34 and 1q11-21, respectively.[53,54] Identification of the abnormal gene products associated with these muscular dystrophies will likely reveal additional proteins involved in the pathogenesis of the limb-girdle muscular dystrophies.

Congenital Muscular Dystrophies

Congenital muscular dystrophies (CMDs) are a group of autosomal recessive disorders that share many clinical features, such as neonatal onset of severe weakness, elevated serum CK levels, and myopathic muscle degeneration as determined by light microscopy.[9] CMDs are also clinically characterized by delayed motor milestones, severe and early contractures, and joint deformity.[40]

According to Kunkel,[33] two broad groups of CMDs can be distinguished based on the presence or absence of abnormalities of brain formation identified during neuroimaging studies or on autopsy examination. The first group of CMDs, or "classical" CMD, includes children with "pure" CMD, but without clinically apparent brain dysfunction or malformations. A different review of CMDs classifies this group as CMD I.[55] The clinical features within this group are very heterogeneous, but these CMDs may be subclassified based on the presence or absence of α2-laminin (merosin). Patients with α2-laminin deficiencies have a more severe clinical presentation, higher serum CK values, and a worse prognosis for ambulation than α2-laminin-positive patients.[33] LAMA2, the gene encoding α2-laminin has been mapped to chromosome 6q2.[56]

In the second group of CMDs, affected individuals have central nervous system involvement including mental retardation, malformations of the brain, and clinical involvement of the eyes. This group includes Fukuyama congenital muscular dystrophy (FCMD), muscle-eye brain disease, and Walker-Warburg syndrome,[33,57] which have also been classified as CMD II, III, and IV, respectively.[55] The gene mutated in FCMD was identified and shown to encode a novel protein of unknown function named fukutin.[35]

Emery-Dreifuss Muscular Dystrophy

Emery-Dreifuss muscular dystrophy (EDMD) is an X-linked muscle disorder like DMD and BMD. However, the clinical features of EDMD are quite distinct from those of the dystrophinopathies and include unusual elbow and spine contractures, proximal arm and distal leg distribution of weakness, no pseudohypertrophy, and sometimes-lethal cardiac arrhythmias.[9] Although the predominant form of (EDMD) exhibits X-linked recessive inheritance (X-EDMD), a rare autosomal dominant form has been reported (AD-EDMD). Linkage studies mapped the gene locus for X-EDMD and AD-EDMD to Xq28 and 1q21, respectively. The genes associated with these forms of EDMD were found and their protein products were identified as nuclear membrane proteins: emerin for X-EDMD; and, lamin A and C for AD-EDMD.[58]

Myotonic Dystrophy

Myotonic dystrophy (DM, incidence 13.5 per 100,000 live births) is the predominant form of adult muscular dystrophy, making the disorder the second most common muscular dystrophy in the entire population. DM is a dominantly inherited disorder that affects males and females equally. DM typically presents with subtle facial muscle and distal limb muscle weakness, as well as impaired relaxation of muscle after 20 years of age. Characteristic facial changes, such as low-set ears, a hatchet chin, and ptosis, are also common clinical features. DM is a multisystem disorder characterized by multiple medical problems including muscle weakness plus dysarthria, subtle muscle stiffness due to myotonia, and cardiac conduction system defects. The disease is progressive and can lead to significant disability. Severe cases of DM have a high incidence of presenile cataracts, testicular atrophy, diabetes, kidney failure, early frontal balding in males, and intellectual impairment. A second more severe, congenital form of DM has been characterized and its clinical features include general hypotonia, respiratory distress at birth, and delayed motor and cognitive development.[9,59]

The complex phenotype of myotonic dystrophy results from the expansion of a CTG repeat in the 3' untranslated region of the gene encoding a serine-threonine protein kinase named myotonin or muscular dystrophy protein kinase (DMPK). In DM, the levels of DMPK protein are reduced due to the retention of abnormal DMPK RNA within the nucleus. However, data suggest that DM is not simply caused by a biochemical deficiency or abnormality in DMKP protein. Instead, the expanded repeat appears to silence the expression of a flanking gene, *SIX5*, which encodes a transcription factor. Recent data also suggest that the pathogenic effect of the DM mutation may be mediated by the mutant mRNA since transcripts with expanded CUG repeats can be toxic to muscle fibers.[42,43,44,59]

Diagnosis of Muscular Dystrophies

Prior to the elucidation of the molecular biology of muscular dystrophies, the wide variety of clinical presentations associated with these disorders caused difficulties in the classification of this group. In addition, the extensive overlap of signs and symptoms among the dystrophies provided a challenge to the physician who had to be able to diagnosis the dystrophies with few tools beyond clinical observation and analysis of biopsied or autopsied muscle samples. With the identification of the gene loci and gene products associated with the muscular dystrophies, advances in the devel-

opment of molecular genetic techniques are providing the means by which a clinician can now clearly differentiate between some of the dystrophies and diagnose these muscle disorders with greater accuracy. Currently, the most reliable diagnostic tools used are: (i) genetic analysis techniques, such as the polymerase chain reaction; and, (ii) biochemical procedures, including immunohistochemistry. Because categories within the group of muscular dystrophies can now be confirmed by gene or protein analysis, clinical correlates are beginning to emerge which help to define the various subgroups.[40] In addition, molecular genetic techniques have made prenatal diagnosis of some of the muscular dystrophies available, thereby increasing the effectiveness of genetic counseling and making the prevention of most forms of muscular dystrophy possible.[60]

Tools for the Diagnosis of the Muscular Dystrophies

Although clinical observations, family history, muscle biopsies, and biochemical tests, such as serum creatine kinase (CK) measurements, still remain important tools for the diagnosis of the muscular dystrophies, genetic and protein analyses are becoming increasingly important in diagnosing the major muscular dystrophies. Some of the procedures that are now being used in gene and protein analyses are listed below.

Genetic Analysis

Genetic analysis in the diagnosis of muscular dystrophies attempts to identify mutations in the gene associated with the suspected type of muscular dystrophy. Methods for the detection of large rearrangements of a gene involved in muscular dystrophy, such as the dystrophin gene, include the polymerase chain reaction (PCR), Southern blotting, reverse transcription PCR, and fluorescent in situ hybridization.[61] At present, only PCR and Southern blotting are routinely used in most diagnostic laboratories. These procedures require small amounts of DNA, usually obtained from a blood sample. The sensitivity and specificity of the tests varies; however, for the dystrophin gene, PCR allows for detection of 98% of all deletions.[62]

Several methods are currently being used for the detection of microlesions in genes, including the dystrophin gene.[63] These methods include single strand conformation polymorphism, heteroduplex analysis, protein truncation test, chemical mismatch cleavage, and denaturing gradient gel electrophoresis.[61] When DMD or BMD has been diagnosed with certainty by protein analysis, but no gene mutations can be identified by PCR or Southern blotting, one of the above tests should to used whenever possible to screen for a mutation in the dystrophin gene.[61]

Protein Analysis

Protein analysis in the diagnosis of muscular dystrophies is based on an understanding of the mutated proteins associated with different forms of muscular dystrophy. The two main methods used are: (i) immunohistochemistry; and, (ii) immunoblotting (Western blotting). Both techniques use labelled antibodies to the specific muscle protein that is abnormally expressed in a particular muscular dystrophy. The immunohistochemical technique first introduced for the diagnosis of DMD[64] is now being widely used to diagnose other types of muscular dystrophies. For example, testing for deficiency of components of the sarcoglycan complex is indicated in dystrophin positive disorders[65] to diagnose the sarcoglycanopathies.

Conclusion

The incredible advances made in defining, classifying, and diagnosing the dystrophinopathies and nondystrophinopathies over the past two decades exemplify the valuable contributions that molecular biological techniques have made to research into genetic diseases, such as the muscular dystrophies. Since the discovery of an association between dystrophin and Duchenne muscular dystrophy, a multitude of additional proteins involved in the pathogenesis of other forms of muscular dystrophies have been identified. In addition, the structure and interactions of many of these proteins have been elucidated, providing a comprehensive understanding of the dystrophin-associated protein complex. New genes and gene products associated with the muscular dystrophies are likely to be identified in the upcoming years. However, much of the research in the field must now focus on understanding the functional characteristics of these protein complexes in both normal physiological and pathological states. Just as knowledge into the structure of the muscle cell membrane has allowed for the evolution of improved diagnostic techniques, a better understanding of the function of these genes and proteins will promise new treatments and therapies for this large group of muscle disorders.

References

1. Emery AEH. (1998). The muscular dystrophies. *BMJ.* 317: 991-995.
2. Ozawa E, Noguchi S, Mizuno Y, et al. (1998). From dystrophinopathy to sarcoglycanopathy: evolution of a concept of muscular dystrophy. *Muscle Nerve.* 21: 421-438.
3. Walton JN and Nattrass FJ. (1954). On the classification, natural history and treatment of the myopathies. *Brain.* 77: 169-231.
4. Beggs AH. (1997). Dystrophinopathy, the expanding phenotype. Dystrophin abnormalities in X-linked dilated cardiomyopathy. *Circulation.* 95: 2344-2347.
5. Koenig M, Monaco AP, and Kunkel LM. (1988). The complete sequence of dystrophin predicts a rod-shaped cytoskeletal protein. *Cell.* 53: 219-226.
6. Campbell KP and Kahl SD. (1989). Association of dystrophin and an integral membrane glycoprotein. *Nature.* 338: 259-262.
7. Ervasti JM and Campbell, KP. (1991). Membrane organization of the dystrophin-glycoprotein complex. *Cell.* 66: 1121-1131.
8. Worton R. (1995). Muscular dystrophies: diseases of the dystrophin-glycoprotein complex. *Science.* 270: 755-776.
9. Brown, RH. (1997). Dystrophin-associated proteins and the muscular dystrophies. *Ann Rev Med.* 48: 457-466.
10. Ervasti JM and Campbell KP. (1993). A role for the dystrophin-glycoprotein complex as a transmembrane linker between laminin and actin. *J Cell Biol.* 122: 809-823.
11. Ibraghimov-Beskrovnaya, O, Ervasti JM, Leveille, CJ, et al. (1992). Primary structure of dystrophin-associated glycoproteins linking dystrophin to the extracellular matrix. *Nature.* 355: 696-702.
12. Roberds SL, Anderson RD, Ibraghimov-Beskrovnaya O, *et al.* (1993). Primary structure and muscle-specific expression of the 50-kDa dystrophin-associated glycoprotein (adhalin). *J Biol Chem.* 268: 23739 - 23742.
13. Lim LE, Duclos F, Broux O, *et al.* (1995). Beta-sarcoglycan: characterization and role in limb-girdle muscular dystrophy linked to 4q12. *Nat Genet.* 11: 257-265.
14. Noguchi S, McNally EM, Ben Othmane K, *et al.* (1995). Mutations in the dystrophin-associated protein gamma-sarcoglycan in chromosome 13 muscular dystrophy. *Science.* 270: 819-822.
15 Nigro V, Piluso G, Belisto A, *et al.* (1996). Identification of a novel sarcoglycan gene at 5q33 encoding a sarcolemmal 35 kDa glycoprotein. *Hum Mol Genet.* 5: 1179-1186.
16 Crosbie RH, Lebakken CS, Holt KH, *et al.* (1999). Membrane targeting and stabilization of sarcospan is mediated by the sarcoglycan subcomplex. *J Cell Biol* 145: 153-165.
17. Ettinger AJ, Feng G, and Sanes JR. (1997). e-sarcoglycan, a broadly expressed homologue of the gene mutated in limb-girdle muscular dystrophy 2D. *JBC* 272: 32534-32538.
18. Straub V, Ettinger AJ, Durbeej M, *et al.* (1999). Epsilon-sarcoglycan replaces alpha-sarcoglycan in smooth muscle to form a unique dystrohpin-glycoprotein complex. *JBC* 274: 27989-27996.
19. Suzuki A, Yoshida M, Yamamoto H, *et al.* (1992). Glycoprotein-binding site of dystrophin is confined to the cysteine-rich domain and the first half of the carboxy-terminal domain. *FEBS Lett.* 308: 154-160.
20. Ozawa E, Yoshida M, Suzuki A, *et al.* (1995). Dystrophin-associated proteins in muscular dystrophy. *Hum Mol Genet.* 4: 1711-1716.
21. Sadoulet-Puccio HM, Khurana TS, Cohen JB, *et al.* (1996). Cloning and characterization of the human homologue of a dystrophin related phosphoprotein found at the Torpedo electric organ post-synaptic membrane. *Hum Mol Genet.* 5: 489-496.

Sotgia F, Bruno C, *et al.* (1998). Mutations in the caveolin-3 gene cause dominant limb girdle muscular dystrophy. *Nat Genet.* 18: 365-368.

Reid MD, Bredt DS, *et al.* (1994). Nitric oxide in skeletal muscle. 372: 546-548.

GA, Dunxtrenko GM, Winkelmann JC, *et al.* (1992). Dystrophin colocal beta spectrin in distinct subsarcolemmal domains in mammalian skele muscle. *J Cell Biol.* 117: 997-1005.

Morett C, Beltrame F, Marcenaro G, *et al.* (1992). Dystrophin at the plasma membrane of human muscle fibers shows a costameric localization. *Neuromusc Disord.* 2: 99-109.

Carlson CG. (1998). The dystrophinopathies: an alternative to the structural hypothesis. *Neurogenet Dev.* 5: 3-15.

Yang B, Ibraghimov Beskrovnaya O, Moomaw CR, *et al.* (1994). Heterogeneity of the 59 kDa dystrophin-associated protein revealed by cDNA cloning and expression. *J Biol Chem.* 269: 6040-6044.

Song KS, Li S, Okamoto T, *et al.* (1996). Co-purification and direct interaction of Ras with caveolin, an integral membrane protein of caveolae microdomains. Detergent free purification of caveolae microdomains. *J Biol Chem.* 271: 9690-9697.

Sattler R, Xiong Z, Lu WY, *et al.* (1999). Specific coupling of NMDA receptor activation to nitric oxide neurotoxicity by PSD-95 protein. *Science.* 284: 1845-1848.

M. Sheng and Pak DT. (1999). Glutamate receptor anchoring proteins and the molecular organization of excitatory synapses. *Ann N Y Acad Sci.* 868: 483-493.

Kinbara K, Sorimachi H, Ishiura S, *et al.* (1997). Muscle-specific calpain, p94, interacts with the extreme C-terminal region of connectin, a unique region flanked by two immunoglobulin C2 motifs. *Arch Biochem Biophys.* 342: 99-107.

Sorimachi H, Kinbara K, Kimura S, *et al.* (1995). Muscle-specific calpain, p94, responsible for limb girdle muscular dystrophy type 2A, associates with connectin through IS2, a p94-specific sequence. *J BiolChem.* 270: 31158-31162.

Bonnemann CG, McNally EM, and Kunkel LM. (1996). Beyond dystrophin: current progress in the muscular dystrophies. *Curr Opin Pediatr.* 8: 569-582.

Anderson LV, Davison K, Moss JA, *et al.* (1999). Dysferlin is a plasma membrane protein and is expressed early in human development. *Hum Mol Genet.* 8: 855-861.

Hayashi YK, Chou FL, Engvall E, *et al.* (1998). Mutations in the integrin alpha7 gene cause congenital myopathy. *Nat Genet.* 19: 94-97.

Tripodis N, Kypreos K, Lorenz JN, *et al.* (1998). Early induction of myocardial heat shock protein 25 expression by amino-terminal atrial natriuretic peptide in vivo. *J Mol Cell Cardiol.* 30: 1519-1526.

Tananapazir L, Dalakas MC, Cyran F, *et al.* (1993). Missense mutations in the beta-myosin heavy-chain gene cause central core disease in hypertrophic cardiomyopathy. *Proc Natl Acad Sci U S A.* 90: 3993-3997.

Laing NG, Wilton SD, Akkari PA, *et al.* (1995). A mutation in the alpha tropomyosin gene TPM3 associated with autosomal dominant nemaline myopathy. *Nat Genet.* 9: 75-79.

Nagano A, Koga R, Ogawa M, *et al.* (1996). Emerin deficiency at the nuclear membrane in patients with Emery-Dreifuss muscular dystrophy. *Nat Genet.* 12: 254-259.

Bonne G, DiBarletta MR, Varnous S, *et al.* (1999). Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nat Genet.* 21: 285-288.

Tomlo D and Minetti C. (1999). Muscular dystrophies: alterations in a limited number of cellular pathways? *Curr Opin Genet Biochem.* 9: 275-282.

Wijmenga C, Frants RR, Brouwer OF, *et al.* (1990). Location of facioscapulohumeral muscular dystrophy gene on chromosome 4. *Lancet.* 336: 651-653.

Felisari G, Martinelli BF, Bardoni A, *et al.* (2000). Loss of Dp140 dystrophin isoform and intellectual impairment in Duchenne dystrophy. *Neurology* 55: 559-564.

Brook JD, McCurrach ME, Harley HG, *et al.* (1992). Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. *Cell.* 68: 799-808.

Mankodi A, Logigian E, Callahan L, *et al.* (2000). Myotonic dystrophy in transgenic mice expressing an expanded CUG repeat. *Science.* 289: 1769-1772.

Matsuo M. (1996) Duchenne/Becker muscular dystrophy: from molecular diagnosis to gene therapy. *Brain Dev.* 18: 167-172.

Walton JN. (1955). On inheritance of muscular dystrophy. *Ann Hum Genet.* 20: 1.

Samaha FJ and Quinlan JG. (1996). Dystrophinopathies: clarification and complication. *J Child Neurol.* 11: 13-20.

Hoffman EP, Fischbeck KH, Brown RH, *et al.* (1988). Characterization of dystrophin in muscle-biopsy specimens from patients with Duchenne's or Becker's muscular dystrophy. *N Engl J Med.* 318: 1363-1368.

Bushby KM and Beckmann JS. (1992). The limb-girdle muscular dystrophies--proposal for a new nomenclature. *Neuromus Disord.* 2: 337-343.

Bushby KM. (1999). Making sense of the limb-girdle muscular dystrophies. *Brain.* 122: 1403-1420.

Moreira ES, Vainzof M, Marie SK, *et al.* (1997). The seventh form of autosomal recessive limb girdle muscular dystrophy is mapped to 17q11-12. *Am J Hum Genet.* 61: 151-159.

Weiler T, Greenberg CR, Zelinski T, *et al.* (1998). A gene for autosomal recessive limb girdle muscular dystrophy in Manitoba Hutterites maps to chromosome region 9q31-q33: evidence for another limb-girdle muscular dystrophy locus. *Am J Hum Genet.* 63: 140-147.

Speer MC, Yamaoka LH, Gilchrist JH, *et al.* (1992). Confirmation of genetic heterogeneity in limb-girdle muscular dystrophy: linkage of an autosomal dominant form to chromosome 5q. *Am J Hum Genet.* 50: 1211-1217.

van der Kooi AJ, van Meegen M, Ledderhof TM, *et al.* (1997). Genetic localization of a newly recognized autosomal dominant limb-girdle muscular dystrophy with cardiac involvement (LGMD1B) to chromosome 1q11-21. *Am J Hum Genet.* 60: 891-865.

Leyten QH, Gabreel FJ, Renier WO, *et al.* (1996). Congenital muscular dystrophy: a review of the literature. *Clin Neurol Neurosurg.* 98: 267-280.

Hillaire D, Leclerc A, Faure S, *et al.* (1994). Localization of merosin-negative congenital muscular dystrophy to chromosome 6q2 by homozygosity mapping. *Hum Mol Genet.* 3: 1657-1661.

Voit T. (1998). Congenital muscular dystrophies: 1997 update. *Brain Dev.* 20: 65-74.

Funakoshi M, Tsuchiya Y, and Arahata K. (1999). Emerin and cardiomyopathy in Emery-Dreifuss muscular dystrophy. *Neuromus Disord.* 9: 108-114.

Korade-Mirnics Z, Babitzke P, and Hoffman E. (1998). Myotonic dystrophy: molecular windows on a complex etiology. *Nuc Acids Res.* 26: 1363-1368.

Abbs S. (1996). Prenatal diagnosis of Duchenne and Becker muscular dystrophy. *Prenat Diag.* 16: 1187-1198.

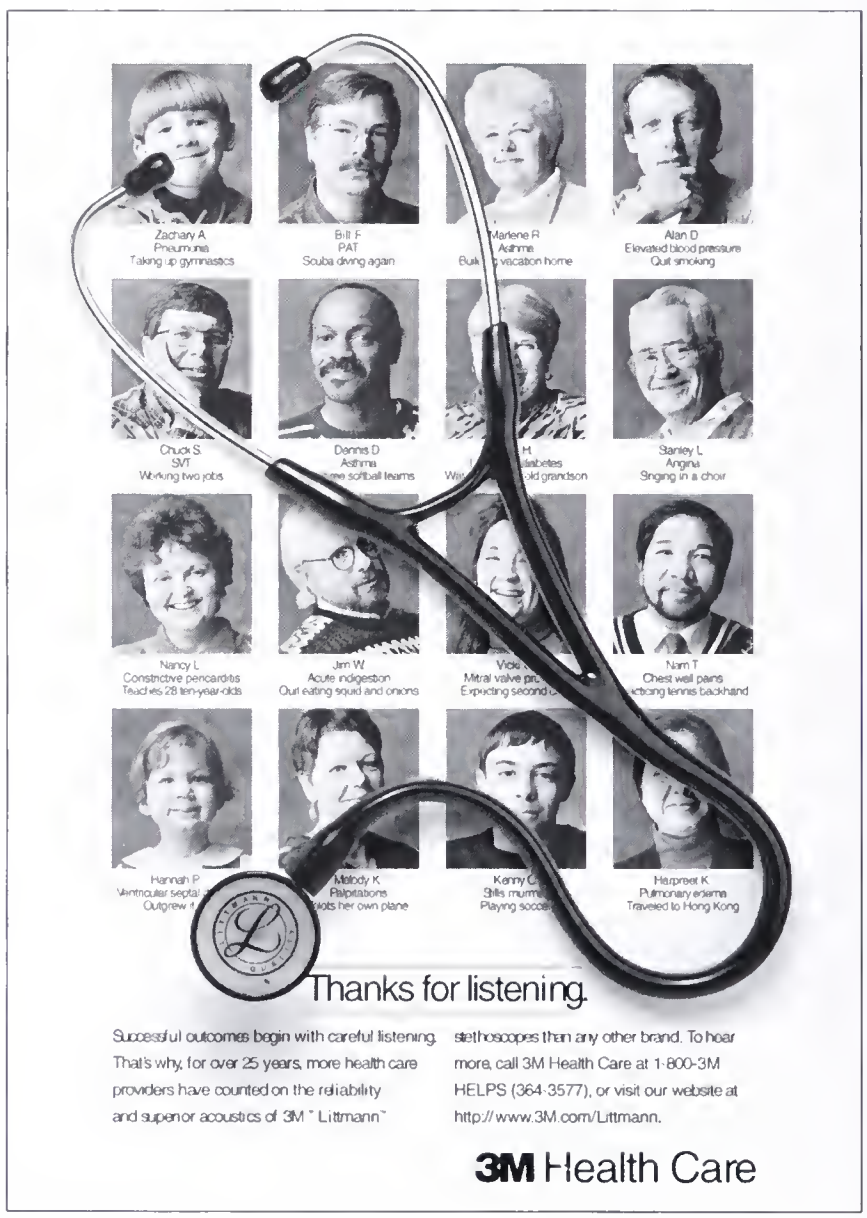
van Essen AJ, Kneppers AL, van der Hout AH, *et al.* (1997). The clinical and molecular genetic approach to Duchenne and Becker muscular dystrophy: an updated protocol. *J Med Genet.* 34: 805-812.

Abbs S, Yau SC, Clark S, *et al.* (1991). A convenient multiplex PCR system for the detection of dystrophin gene deletions: a comparative analysis with cDNA hybridisation shows mistypings by both methods. *J Med Genet.* 28: 304-311.

Roberts RG, Bobrow M, and Bentley DR. (1992). Point mutations in the dystrophin gene. *Proc Natl Acad Sci U S A.* 89: 2331-2335.

Zubrzycka-Gaarn EE, Bulman DE, Karpati G, *et al.* (1998). The Duchenne muscular dystrophy gene product is localized in sarcolemma of human skeletal muscle. *Nature.* 333: 466-469.

Anderson LV. (1996). Optimized protein diagnosis in the autosomal recessive limb-girdle muscular dystrophies. *Neuromusc Disord.* 6: 443-446.



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Phantom Menace: The Mystery of Phantom Limb Pain: A Case Report and Review of the Literature

Sonja Alexandra McVeigh, BSc*

Abstract

A significant number of patients with amputations experience phantom limb pain. It is a phenomenon that had been reported as early as the sixteenth century. Notably, in up to 70% of patients, phantom pain persists 25 years after the amputation. A significant medical implication of phantom pain is that the phantom limb becomes a considerable impediment to successful rehabilitation. Neuromas within the stump and spinal cord hyperexcitability are previously proposed mechanisms for this phenomenon that have since been disproven. More recent theories are based upon the concepts of a neuromatrix or cortical remapping, the latter of which challenges the generally accepted notion that the neural connections laid down in fetal life are fixed, and therefore has potential implications for the possibility of future treatment of more central deafferentation processes, including stroke. Currently, few treatments for phantom pain have been proven to be effective. Amitriptyline (Elavil™) has been the most studied tricyclic antidepressant for phantom pain and is recommended as the first choice for treatment. Other pharmacologic agents reported to possess varying efficacies for the treatment of phantom limb pain include antiarrhythmics, anticonvulsants, opioids, GABA receptor agonists, N-methyl-D-aspartate (NMDA) receptor antagonists, adrenoceptor agonists, and calcitonin.

> *Truly, it is a thing wondrous, strange, and prodigious which will scarce be credited, unless by such have seen with their own eyes and heard with their own ears, the patients who many months after cutting away the leg, grievously complained that they yet felt exceedingly great pain in that leg so cut off.*
>
> *-Ambrose Paré (1510 - 1590) French military surgeon*[1]

Mr. L.W., a 64 year old patient, was interviewed four months after his left below knee amputation (BK-1) secondary to peripheral vascular disease attributed to advanced Type I diabetes mellitus. Seven years previously, he had a right BK-1 (also due to his diabetes mellitus) for which he has a prosthesis. Comorbidities included: diabetic nephropathy, for which he had been on hemodialysis for the past two years; ischemic heart disease; hypertension; bowel ischemia with subsequent ileostomy; and diabetic retinopathy. He had experienced delayed wound healing with his recent left BK-1, with complete healing of approximately three months duration. At the time of the interview, he had minimal stump edema. He reported no stump pain. However, he did describe intermittent "sharp" phantom pain in his toes, primarily in both large toes, that ranged in frequency between once per day to once every few months. The onset of the phantom pain occurred in each toe "shortly after" the respective amputations. Between the episodes of phantom pain, he had solely phantom limb sensation, whereby he could feel the presence of both his feet.

During peacetime, the primary indication for amputation is peripheral vascular disease (PVD). In fact, 60% of amputations are attributed to PVD, and half of these patients also have diabetes mellitus.[2] The majority of patients with amputations are elderly, and therefore the associated physiological phenomenon of "phantom limb" pain is most frequently experieneed by this population, and many present with several eo-morbidities.[2] Phantom pain may not only be exerueiating for the elderly patient, but may also reduee self-esteem, impair the ability to perform aetivities of daily living, limit independenee, and can lead to depression.[2] Thus, investigation into the pathophysiology of phantom limb pain and the development of rational therapies is especially important to this population. Any intervention, particularly in elderly patients with complex medieal issues, must be balaneed against potential risks, side effects and emplieations.

Phantom limb pain is a phenomenon reported as early as the sixteenth eentury.[1] At that time, Freneh military surgeon Ambroise Paré reeognized the peculiar faet that patients, often months or even years following their amputation, complained of agonizing pain in the region of the removed limb.[3] Subsequently, there have been many elinieal examples of phantom pain. Often, through an unexplained eoneept known as "imprinting", the limb may feel as if it is immobilized in the position that it was in at the time of a traumatie amputation. For example, a motoreyelist who had forcefully gripped his hands onto the handlebars at the moment of impact in a motor vehiele aeeident reported his phantom pain as a elenehed hand with the fingers bent over the thumb and digging into the palm.[4] Another patient who had lost his hand when a grenade which he was holding detonated reported a lingering and intense phantom pain of explosive quality.[4] Phantom pain discomfort ean range in intensity from a cramp in the ealf, to the toes feeling that they are "being seared by a red hot poker".[5] There have also been reports of phantom pain resembling ehronie painful sensations, such as a painful ulcer or bunion, in the limb prior to the amputation.[5] Melzack notes it is striking that these patients are not simply reealling sueh feelings, but are, in fact, experieneing them

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with the details of an ongoing sensation;[5] indeed, the experiences are perceived as real.

A significant medical implication of phantom pain is that the phantom limb becomes a considerable impediment to successful rehabilitation.[3] The incidence of severe pain is such that it constitutes a significant clinical problem: up to 70% of patients with phantom pain report its persistance up to 25 years after the amputation.[6] In fact, pain is present in the first week after amputation in 50-75% of patients.[3] The pain is commonly localized distally in the phantom limb; one study of 64 above-knee amputation patients with phantom pain showed that 66% had pain in the foot or toes, 39% had additional pain in the calves, while only 6% had pain also in the quadriceps region.[3,10] However, there is great discrepancy among the reports of overall incidence of phantom pain (ranging from 2 to 97%[7]), making the true burden of phantom pain difficult to ascertain. Several explanations have been proposed for this wide variation in incidence. Firstly, there is disagreement over what may be included in the definition of phantom limb pain. The International Association for the Study of Pain (1986) defines the condition as "pain referred to a surgically removed limb or portion thereof".[7] However, there have been many reports of phantom pain subsequent to accidental amputation, as well as in patients with paraplegia, brachial plexus avulsion, and even in those with congenital limb deficiencies.[5,7] Secondly, differences in patient pain threshold and pain tolerance as well as variation in the methods by which phantom pain sensations are portrayed and recorded, make a distinct definition elusive.[3] Thirdly, the method of eliciting a description of phantom pain is not without bias, since direct questioning is likely to conclude a higher incidence of phantom pain than that determined by waiting for unprompted patients to offer their symptoms.[7]

The incidence of phantom pain specific to the elderly also shows disparity.[2] Historically, behavioural science literature indicated that phantom pain was either a manifestation of an emotional problem or of personality structure; many patients with amputations in earlier years reported that their physicians directly stated that the pain was "just in their heads".[8] Consequently, elderly patients may remain unwilling to divulge that they are experiencing phantom pain for fear of their physician thinking that they may be suffering from a mental illness. In an amputee survey by Sherman *et al.*,[8] the great majority of patients with amputations stated that they feared losing their credibility with their physician by reporting phantom pain. These patients were concerned that any further reporting of stump difficulties would not be taken seriously, especially when a verbal complaint is often the only evidence of a stump problem with the patient. This rationalization could explain the differences in the reported rate of phantom limb pain in the elderly. Indeed, the most recent evidence implies that phantom pain is influenced by psychological factors such as stress and depression, which can aggravate phantom pain.[3,9] Like other chronic pain syndromes, however, there is no convincing evidence that personality disorders play a role in the etiology of phantom pain.[8] Rather, the most recent efforts to explain phantom pain, particularly those by Katz and Melzack[5,10] and Ramachandran and Hirstein,[6] suggest that phantom pain has a very real physiological basis.

The oldest explanation for phantom pain proposes that the remaining nerves at the amputated end of the stump continue to grow into neuromas.[5] These neuromas produce a rapid rate of impulses which travel to the spinal cord, ascend to the thalamus, and then relay to the somatosensory area of the cortex.[5,7,9,11] This concept led to the theory of a peripheral origin of phantom pain. However, attempts to permanently abolish phantom pain have been unsuccessful. These attempts have included the elimination of afferent input from the stump by administration of local anesthetic[7] and by severing of the nerves immediately proximal to the neuroma from the stump,[5] severing pathways within the spinal cord, and removal of the regions of the thalamus and cortex that receive the removed limb's sensory input.[5] Thus, activity within the stump itself cannot explain phantom pain.

Overactive, spontaneous firing of neurons within the spinal cord was the central theme of another hypothesis for phantom pain. Because these neurons had lost their usual sensory input from the amputated limb, it was reasoned that their resulting hyperexcitability was received by the cortex, thereby causing the perception of phantom pain.[5] This theory was later refuted by observations of phantom pain in the legs of paraplegics who had complete injury to either the thoracic, lumbar or sacral region of their spinal cords. The spinal cord theory could not explain how these nerve impulses, apparently generated below the damaged region of cord, were still able to travel up to the brain.[5,7]

The most recently proposed explanations for the etiology of phantom pain are those of Katz and Melzack[5,10] and Ramachandran and Hirstein.[6] Both theories agree that the phantom limb experience is so complex that higher levels of the nervous system, specifically the brain, must be involved. However, each theory has a unique perspective on the origins of phantom pain.

Melzack postulates that within the brain lies a "neuromatrix" – a network of neurons that responds to sensory input and constantly produces a specific pattern of impulses, called the "neurosignature", which registers that the body is intact.[5] According to this theory, the neuromatrix continues to operate even in the absence of input from an amputated limb, thereby "creating the impression of having a limb even when that limb has been removed".[5] Melzack envisions the neuromatrix to be composed of three brain circuits: the classical sensory pathway, the limbic system pathway responsible for emotion and motivation, and cortical pathways in the parietal lobe essential for the recognition of self.[5] Respectively, these three components potentially account for the sensation of pain, the affective descriptions of phantom limbs as "exhausting" or "penetrating", and the sense that the pain of the limb is actually a part of the patient. Furthermore, Melzack deduces that the neuromatrix must be determined genetically, due to observations that congenital limb deficient patients are also capable of experiencing phantom pain.[13] Little research has been performed to test Melzack's idea. In fact, many studies exploring the causes of phantom pain are methodologically flawed, in that they have small, heterogeneous samples, are non-randomized, lack appropriate control groups, and have short patient follow-up periods.[9,14]

However, Ramachandran and Hirstein[6] have presented the most up-to-date theory of the cause of phantom sensation and pain, and have extensively described their experimental findings. In one experiment, upon touching specific regions in the face of a patient with an amputated left arm, the patient noted a tingling sensation in the fingers of the missing limb. Further investigation showed a systematic one-to-one mapping between specific regions of the face and individual fingers (*i.e.*, cheek to thumb, upper lip to index finger, etc.), and that these relations were stable over 6 months.

The authors postulated that because the map of the hand is adjacent to the face on the sensory homunculus in the cortex, the sensory input from the face may have "invaded" the area of the homunculus normally devoted to the hand. It was proposed that the hand cortical area was overtaken by the facial cortical area because the hand region was no longer receiving sensory input due to the amputation.[3] This theory would also explain why other patients with foot amputations have reported sexual sensations in their missing foot during intercourse: the genital area is located next to the foot area on the homunculus.[4] It is not clear, however, why the sensations are specifically only sexual. This theory may explain why a patient with an amputation can still sense pain in a limb that is physically no longer part of the body; sensory input from adjacent areas on the homunculus may have overtaken the area previously receiving input from the amputated limb. This "theory of cortical remapping", along with several other examples of neural plasticity,[18,19] challenges the widely-held dogma that neural connections established in fetal life are immutable. If this theory is verifed, then the potential to reorganize neural pathways later in life may have implications for treatment of more central deafferentation, such as stroke.[6]

Earlier studies by Sherman *et al.*[15] suggested that many physicians previously considered phantom pain to be "pure imagination", finding that 50-75% of patients with amputations reported phantom pain to their physicians but that only 20% were offered treatment. Although phantom limb pain is now well recognized to be a physiological phenomenon,[4,5,6,9,12,13] the lack of a clearly demonstrated mechanism of causation has hindered the discovery of an effective, long-term treatment for this disorder. Another obstacle to offering effective treatment of phantom limb pain is that although numerous case studies have been reported, there have been few clinical trials investigating definitive treatments for phantom limb pain.[14] The majority of these studies are small, non-randomized, and open-labelled, in addition to having a relatively high placebo response between 30 and 35%.[14,16] A review of the literature indicates that very few studies have been undertaken to estimate the cost of phantom pain both to the patient and the health care system.

Presently, there are several options for treatment of phantom limb pain. However, none have been demonstrated to be permanently effective. Tricyclic antidepressants such as amitriptyline (Elavil™), desipramine (Norpramin™), and maprotiline (Ludiomil™) can be effective in the treatment of both neuropathic pain and phantom pain, although there is a lack of controlled studies looking specifically at their efficacies when used in phantom pain treatment.[2,14] In individual patients with phantom pain, the tricyclic agent doxepin (Sinequan™) has also been shown to be effective, although amitriptyline has been more thoroughly studied in this regard and is recommended as the first treatment choice.[2] Well designed, non-experimental studies, such as comparative, correlative-descriptive and case studies have demonstrated that antiarrhythmics such as lidocaine (Xylocaine™), mexiletine (Mexitil™) and tocainide (Tonocard™) are effective for phantom limb pain.[17] The mechanism suspected in the effectiveness of these drugs is their ability to reduce hyperexcitability in central neurons.[2,17] Anticonvulsants, through reducing high frequency repetitive discharges, are moderately successful in the treatment of phantom limb pain.[2,14] No controlled studies have yet been performed which examine the use of opioids for this disorder, although there have been several reports of their benefit and ability to be well tolerated.[2,14] Other medications noted to diminish phantom limb pain include GABA receptor agonists (*e.g.*, baclofen (Lioresal™)), NMDA receptor antagonists (*e.g.*, ketamine (Ketalar™)), and adrenoceptor agonists.[2,11] Again, there have been few clinical trials evaluating the clincial utility of these agents in the context of phantom limb pain.

Recently, studies have investigated the use of calcitonin for the treatment of phantom limb pain.[14,20] A double-blinded study by Jaeger and Maier[20] looked at 21 individuals with phantom pain in various missing limbs. One week after 200 IU per day of intravenous salmon calcitonin treatment, 90% of patients reported pain relief by at least 50%, and 76% were pain-free. At 24 months, 70% of patients remained free of phantom pain.[14] However, calcitonin given in this manner does have a rare risk of a severe hypersensitivity reaction, and is also associated with nausea and vomiting.[11,14]

Surgery affecting the peripheral or central nervous system invariably generates additional deafferentation, and thus, an increased risk of continuing pain.[2] Therefore, it is recommended that surgery be an option of last resort. Non-pharmacological treatments which have demonstrated varying degrees of success include transcutaneous electrical nerve stimulation (TENS), acupuncture, hypnosis, and spinal cord or deep brain stimulation.[5,14] Nevertheless, approximately half of those with persistent, chronic phantom pain do not respond to any of these interventions.[5]

The phantom limb phenomenon is frequently unrelenting and excruciatingly painful. The pain in the amputated limb often becomes a major obstacle to effective rehabilitation, leading to disruption of daily activities, depression, weight loss, and isolation. In addition to being a challenge for management, the phantom limb phenomenon may cast further doubt about a fundamental assumption in neurology – that neuronal connections established during fetal development are fixed. Effective treatment of phantom pain has thus far eluded neuroscientists, and a solution to this intriguing mystery will require more thorough investigations into its underlying mechanisms.

References

1. Thompson HM. (1998). Pain after amputation: is prevention better than cure? *Br J. Anaesth.* 80: 415-416.
2. Baron R, Wasner G, and Lindner V. (1998). Optimal treatment of phantom limb in the elderly. *Drugs Aging.* 12: 361-376.
3. Jensen T and Rasmussen P. (1992). Phantom pain and other phenomena after amputation. In: *Textbook of Pain.* Wall PD and Melzack R (eds). Churchill-Livingstone: Edinburgh.
4. *The phantom limb.* The Nature of Things, with David Suzuki. January 17, 2000. Produced by The Canadian Broadcasting Corporation.
5. Melzack R. (1992). Phantom limbs. *Sci Am.* 226: 120-126.
6. Ramachandran VS and Hirstein W. (1998). The perception of phantom limbs. *Brain.* 121: 1603-1630.
7. Stannard CF. (1993). Phantom limb pain. *Br J Hosp Med.* 50: 583-586.
8. Sherman RA, Sherman CJ, and Bruno GM. (1987). Psychological factors influencing chronic phantom limb pain: an analysis of the literature. *Pain.* 28: 285-295.
9. Fisher K and Hanspal RS. (1998). Phantom pain, anxiety, depression, and their relation in consecutive patients with amputated limbs. *BMJ.* 316: 903-904.
10. Katz J and Melzack R. (1990). Pain 'memories' in phantom limbs: review and clinical observations. *Pain.* 43: 319-336.
11. Harwood DD, Hanumanthu B, and Stoudemire A. (1992). Pathophysiology and management of phantom limb pain. *Gen Hosp Psychiatry.* 14: 107-118.
12. Borsook D, Becerra L, Fishman S, et al. (1998). Acute plasticity in the human sensory cortex following amputation. *Neuroreport.* 9: 1013-1017.
13. Melzack R, Israel R, Lacroix R, and Schultz G. (1997). Phantom limbs in people with congenital limb deficiency or amputation in early childhood. *Brain.* 120: 1603-1620.
14. Wall GC and Heyneman CA. (1999). Calcitonin in phantom limb pain. *Ann Pharmacother.* 33: 499-501.
15. Sherman RA and Sherman CJ. (1983). Prevalence and characteristics of chronic phantom limb pain among American veterans. *Am J Phys Med.* 62: 227-258.
16. Sherman RA and Tippens J. (1982). Suggested guidelines for treatment of phantom limb pain. *Orthopedics.* 5: 1595-1600.
17. Davis RW. (1993). Successful treatment for phantom pain. *Orthopedics.* 16: 691-694.
18. Kirkwoood A, Rioult MC, and Bear MF. (1996). Experience-dependent modification of synaptic plasticity in visual cortex. *Nature.* 381: 526-528.
19. Wang X, Merzenich MM, Sameshima K, and Jenkins WM. (1995). Remodelling of hand representation in adult cortex determined by timing of tactile stimulation. *Nature.* 378: 71-75.
20. Jaeger H and Maier C. (1992). Calcitonin in phantom limb pain: a double blind study. *Pain.* 48: 21-27.

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The Parasite that Wasn't: A Case of Detached Ciliary Tufts in Cerebrospinal Fluid

Andrea K. Boggild, M.Sc. (0T3), Yael Friedman, M.Sc. (0T3), and Christine A. Sundermann*, Ph.D.

Case Presentation

A 16-year-old girl with congenital hydrocephalus presented to her neurosurgeon with symptoms of ventriculoperitoneal shunt malfunction. Over the previous few days, the patient had become increasingly nauseous and lethargic, and her headache had worsened. On fundoscopic examination, mild papilledema was observed, and retinal venous pulsations were diminished. Her blood pressure was elevated. Cognitive function was intact. Based on history, neurological findings, and a relatively non-compressible catheter valve, imaging of the shunt apparatus and a shunt tap were indicated.

Plain film revealed an intact distal catheter, while CT sean ruled out proximal disconnection. CT sean further revealed a lateral ventriele hydrocephalus, though it was not until shunt tap was performed that the presumed obstruction was localized. A shunt tap, in whieh CSF is eolleeted from a valve reservoir that sits subcutaneously and posteriorly to the auriele, revealed elevated opening pressure, indicative of an obstruction distal to the valve. A sample of CSF was taken for bioehemistry, Gram stain, and eulture.

All bioehemical parameters, ineluding CSF protein and glucose eoneentrations, were normal. Gram stain was negative and a white cell differential uneovered nothing unusual. However, upon microscopie examination of the CSF sample, several unicellular, eiliated "swimming things" were evident in each low-power field. On average, cells measured 16 mm in diameter and had eireumferentially arranged eilia. A second shunt tap was performed and a seeond CSF sample obtained for further mieroseopy. Again, these parasites, with whieh the laboratory teehnicians had no familiarity, were observed. Thus, a parasitologist was ealled in to identify these organisms. What is the differential diagnosis for "swimming things" in eerebrospinal fluid?

Presumptive Diagnosis: Opportunistic Protozoal Infection

There are many organisms, both protozoan and helminthie, that can parasitize the central nervous system. Only a select few, however, fulfill enough of the aforementioned criteria (*i.e.*, unicellularity, ciliary-based motility) to be considered in this ease. The first, a ubiquitous ameboflagellate by the name of *Naegleria fowleri*, causes a fulminant disease called primary amebie meningoencephalitis (PAM) in an extremely small pereentage of people who eome in eontaet with it. As this protozoan tends to inhabit warm, fresh water, most vietims aequire the organism while swimming.[1] Amebae enter the swimmer's nose and aeeess the subarachnoid space of the CNS via the olfactory neuroepithelium and olfactory nerves.[1] Although a typical ineubation period is one to two weeks, onee fever and headaehe are present, a patient has only 72 hours before eoma and death ensue.[1,2] Thus, the possibility of antemortem diagnosis is negligible, with only three survivors reported worldwide.[1] In the parenehymal tissue of the brain, the organism takes on an ameboid feeding form; however, in CSF *Naegleria* exists in its flagellated form, and can therefore appear to "swim". As the patient in this case has no recent history of swimming, and a presentation ineonsistent with PAM, it is unlikely that she is suffering an infeetion with *N. fowleri*. In addition, PAM typieally mimies baeterial meningitis in terms of CSF findings – polymorphonuelear pleocytosis, elevated protein, and very low glueose – none of which were present in this ease.

Unlike *Naegleria fowleri*, triehomonads are not generally assoeiated with CNS infeetion, although there is evidence to suggest that they should be considered when faeed with an unidentified ciliated/flagellated protozoan, regardless of the site of infeetion. Three triehomonads – *Trichomonas tenax, Trichomonas vaginalis*, and *Pentatrichomonas hominis* – have all been reported in assoeiation with or as the primary eause of disease in humans,[3] although typieally, only *T. vaginalis* is thought to be pathogenie. *Trichomonas tenax*, normally a commensal inhabitant of the mouth, ean eause infection of the respiratory tract in people with underlying pulmonary disease.[3] Similarly, *P. hominis*, an enteric triehomonad, is more likely to be reeovered from individuals with symptomatic bowel disease.[3] Triehomonas vaginalis ean eause sexually transmitted triehomoniasis in humans, and is aetually the most eommon parasitie eause of STD.[4] Although trichomonads are known to be site- and, to a eertain extent, host-speeifie,[3] eases of cross-speeies infeetion and reeovery of triehomonads from aberrant loeations have been reported. For example, in 1997, a 34-year-old immunoeompromised man died of acute meningoeneephalitis seeondary to infection with *Tritrichomonas foetus*,[5] an organism that usually infeets the GU system of cattle. How this flagellate was able to survive in the nervous system of a human host remains unexplained, though the patient's immunocompromised state was a likely faeilitating

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factor. Severe meningoencephalitis and ventriculitis were evident at autopsy, and histopathological examination of the meninges revealed many trichomonads, confirmed by SEM to be *T. foetus*.[5] As with a *Naegleria* infection, CSF showed a marked pleocytosis.[5]

The case of *T. foetus*-meningoencephalitis bears particular relevance to the present case as it demonstrates the ability of trichomonads to proliferate in CSF, and induce an inflammatory response that could lead to complications in a shunted individual. Although trichomonad infection should be considered in the differential for the patient reported herein, it is unlikely that the "swimming" organisms isolated were members of this flagellate order. On high-power light microscopic examination, it is very clear that trichomonads lack the circumferential arrangement of flagella noted in this case. In terms of presentation, there was nothing in the patient's history to suggest infection with *T. vaginalis*, or a state of immunosuppression. In addition, her lack of fever, pleocytosis, and elevated CSF protein would argue against protozoal infection.

Single-cellular kinetoplastid flagellates, in particular, the CNS-invading trypanosomes that cause African sleeping sickness, can appear to "swim" in CSF, hence their inclusion in this discussion. Members of the *Trypanosoma brucei* complex can be distinguished from the organisms in this case because of their long, singular polarized flagellum that appears to whip, not beat. Furthermore, transmission of these trypanosomes can only occur through the bite of a tsetse fly vector, endemic to Africa. Although the initial presentation of African sleeping sickness may include headache, nausea, and lethargy, inconsistent parasite morphology and a lack of foreign travel and interaction with insects, precludes this disease from the differential diagnosis.

Pathological Discussion

The second CSF sample was used to prepare wet mounts for Nomarski interference contrast (NIC) microscopy. Both live and formalin-fixed organisms were photographed and measured using an ocular micrometer. As previously mentioned, cells averaged 16 µm in diameter, and had cilia arranged around their periphery (Figure 1). Careful microscopic examination of cells revealed an absence of nuclei, and conventional ciliate culture medium inoculated with CSF failed to grow these ciliates.

To summarize, the "swimming things" found in this patient's CSF were devoid of nuclei and failed to grow *in vitro*. Although their size was in the range of both *Naegleria* and trichomonads, they did not resemble any ciliated or flagellated protozoan known to the parasitologist. Coupled with a normal biochemical profile of CSF and the process of elimination, these unique morphological data led the team to a new differential diagnosis: detached ciliary tufts of unknown origin.

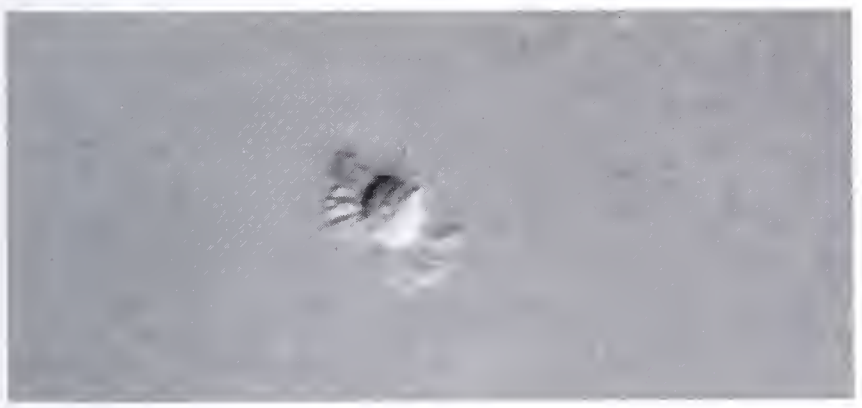

Figure 1. *Nomarski interference contrast micrograph of a ciliated cell fragment isolated from the CSF of a young patient. Note the circumferential arrangement of cilia (arrows). Bar = 16 µm.*

Detached Ciliary Tufts

Ciliated epithelia are common throughout the respiratory and genital tracts of humans. Ciliated cells also line the tympani, Eustachian tubes, and ventricles of the brain. At any of these sites, ciliated cells have the potential to detach by constricting and severing their luminal portions, leaving behind their nucleus and basal cytoplasm.[6] Thus, anuculeate apical fragments of ciliated cells can be a non-pathologic finding in many body fluids.[6] Although the nucleus is generally retained basally, mitochondria are pinched off with the apical cytoplasm, allowing the cell fragment to remain motile for several days.[7] The vigorous ciliary motion that detached ciliary tufts (DCTs) can exhibit in wet mount, creates a diagnostic dilemma of sorts as it emulates that of ciliated protozoa.[6] As evidenced by this case and others,[6-10] DCTs can be easily confused with members of the protozoa.

DCTs are found most frequently in nasal secretions, sputum, and cervicovaginal smears;[6] they are also a common finding in bronchoalveolar lavage.[11] Although the formation of DCTs has been unequivocally linked to respiratory viral infection, it has yet to be demonstrated that DCTs have pathologic significance in any other circumstance.[6] The term ciliocytophthoria (CCP) has been used to describe DCTs that occur in respiratory tract specimens, and because of the established pathologic connotation, the term should only be applied in this context.[6] Unlike CCP, DCTs in cervicovaginal smears and peritoneal dialysates of women result from ciliated oviduct epithelium undergoing a normal, cyclic exfoliation[12] (Figure 2). Thus, their presence in these fluids should be construed not as a pathologic finding, but a physiological one.[6,12] Not surprisingly, post-menopausal women and men undergoing continuous ambulatory peritoneal dialysis (CAPD) are not likely to have DCTs in their effluent.[9] To our knowledge there are no prior reports of DCTs found in CSF. To recap, the finding in body fluids of ciliated cell fragments up to 15 µm in diameter and lacking internal structure, should be diagnostic for DCTs[6]. Parasitic infection can be further excluded by an inability to culture these "ciliates" *in vitro*.

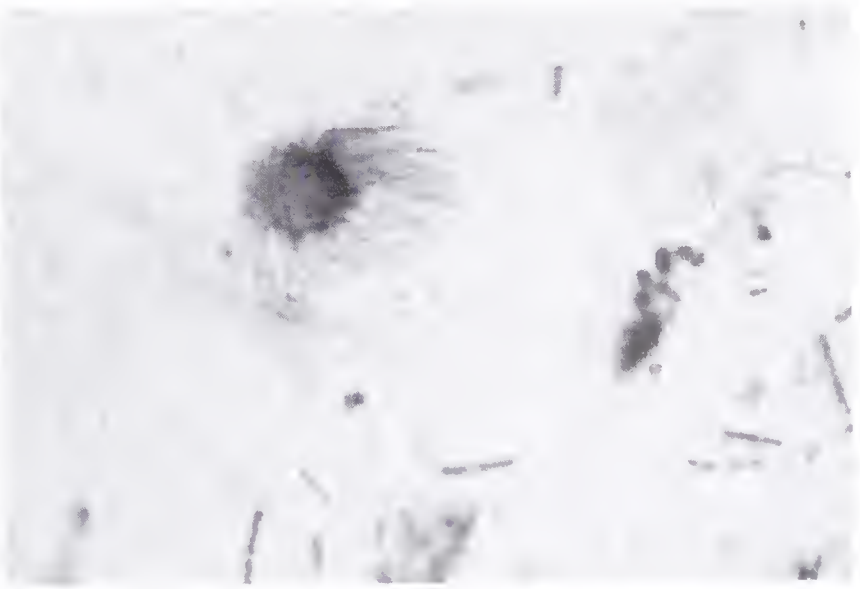

Figure 2. *Detached ciliary tuft from a Papanicolaou-stained smear. Photograph reproduced with permission from Atlas of Human Parasitology, 4th ed. (Ash and Orihel, eds), p. 371.*

The patient reported herein has a CSF shunt, there are two possible portals through which DCTs could have accessed the shunt reservoir: the ventricular end and/or the peritoneal end of the catheter. In this particular shunt apparatus, the proximal catheter passes from a cerebral ventricle (typically lateral) to the valve reservoir via a cranial burr hole.[13] From the valve, the distal portion of the shunt catheter continues along a subcutaneous tunnel until it terminates in the peritoneal cavity.[13] Given this shunt anatomy, there are also two potential sources of DCTs in this patient. First, the DCTs isolated from her shunt reservoir could have arisen from the cerebral ependyma. Alternatively, DCTs of oviduct origin could have entered the peritoneal cavity and accessed the shunt reservoir through retrograde migration. Compelling arguments can be made to support either of these possibilities.

Support for Ependymal Origin of DCTs

Numerous investigations into the causes of proximal shunt malfunction have consistently demonstrated choroid plexus and ependyma to be common sources of obstructive agents.[14-16] In fact, choroid plexus appears to be the most common cause of ventricular catheter obstruction reported.[14] In their examination of 91 ventricular catheter ends, Sekhar *et al.* (1982) found choroid plexus to be the obstructive material in 35 catheters, and ependyma in 15.[14] The prevailing notion is that if proximal catheter inlets are in contact with choroid plexus and/or ependyma (after normalization of ICP and ventricular size), then the tissue can grow into and eventually occlude the catheter lumen.[15] That only a few of the 40-50 small catheter inlets need be patent to maintain adequate CSF flow[16] suggests that ependymal tissue could be present in the shunt catheter without causing obstruction. In light of ependymal morphology (Figure 3), it is conceivable that cell fragments could detach and, because of proximity, easily enter the catheter lumen, hence their discovery in the shunt reservoir. Of particular interest to this case is the finding of choroid plexus, along with other embolic materials, as a cause of distal catheter obstruction (*i.e.*, peritoneal end).[14] That cells of the ventricular lining can be found so far distally substantiates their ability ("intentional" or otherwise) to enter the shunt apparatus, migrate along a flow gradient, and potentially cause obstruction. Although this scenario is plausible, that DCTs are merely cell fragments lacking certain identity cues, make it difficult to localize their site of origin. Therefore, the possibility that her DCTs were from another anatomic locale must be considered.

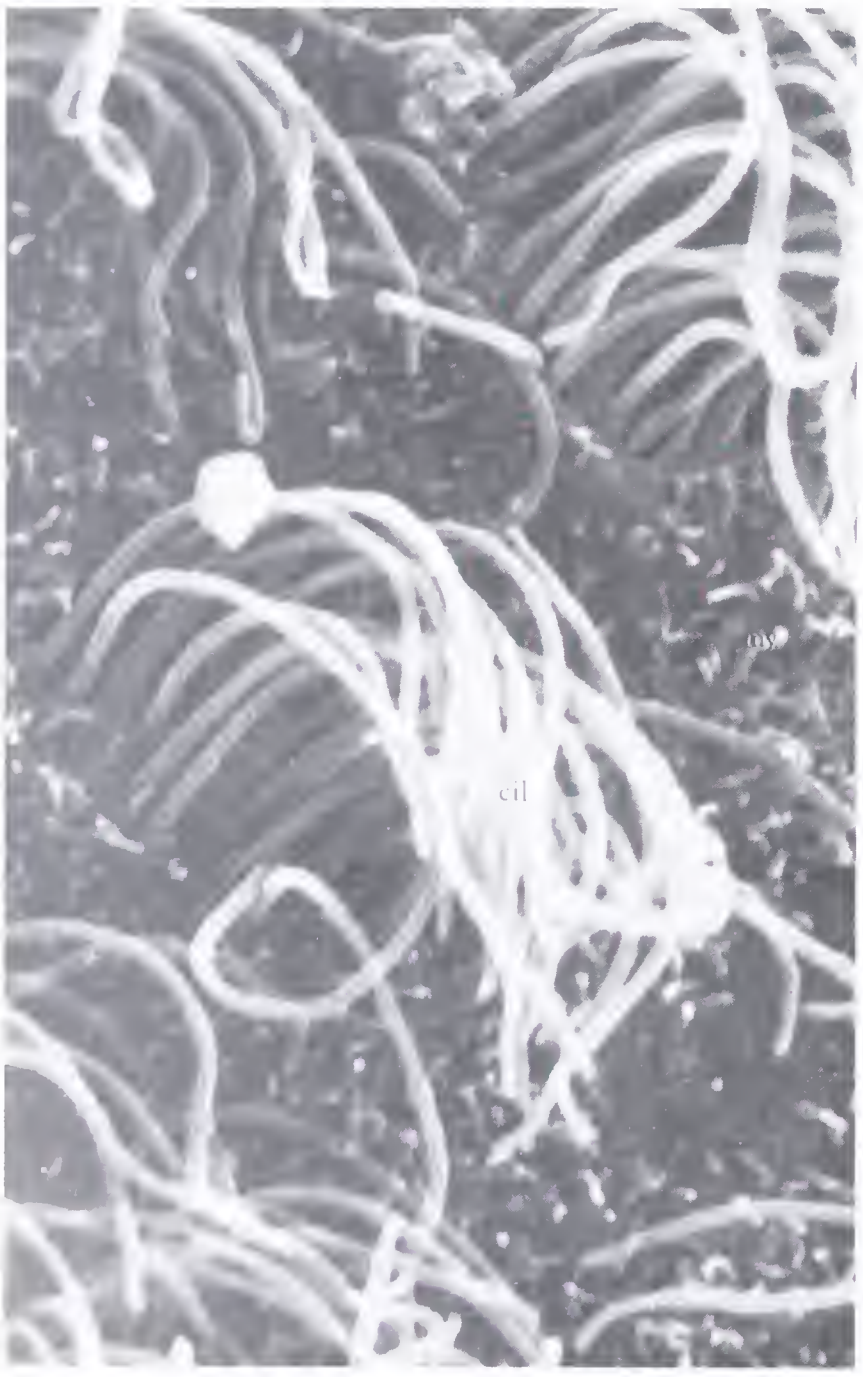

Figure 3. *Scanning electron micrograph of ciliated ependymal cells lining the ventricular surface. Photograph reproduced with permission from Fine Structure of the Nervous System, 3rd ed (Peters, Palay, and Webster, eds), p. 317.*

Support for Oviduct Origin of DCTs

In terms of morphology, the DCTs isolated from this patient very closely resemble those known to be oviduct epithelial cells (compare Figures 1 and 2). Unfortunately, as this is the first reported case to intimate ependymal DCTs, we are lacking a comparison photograph. Clearly, the literature supports an oviduct origin,[6-10,17] and in this patient, there is a very reasonable explanation of how oviduct DCTs could be present in CSF. Since 1986, DCTs have been found in the peritoneal washings of 25 women, most of whom were of reproductive age. In most of the case reports, DCTs were a surprising, incidental finding.[6,8,9,10] Although there exists no evidence that ciliated cells shed into the peritoneal cavity elicit an inflammatory response,[7] in a shunted individual such as this patient, one must be cognizant that oviduct DCTs can be formed with each menstrual cycle, and can thus make their way into the shunt catheter lumen. Whether or not they cause obstruction in motile form, or can withstand the shunt fluid dynamics remains to be determined.

Patient Outcome

After the first two shunt taps, the patient's blockage appeared to resolve spontaneously without neurosurgical intervention. Her ICP normalized and symptoms regressed. She was discharged home and monitored over the next several weeks by her family physician, with no recurrence of symptoms. It was not determined if the DCTs found in the patient's CSF were actually causing the obstruction that led to her admission. Commonly, distal obstruction is attributed to shunt contact with omentum.[13] Despite the possibility that DCTs may have been an incidental finding in this case, it raises the issue of awareness. Clearly, laboratory technicians and other medical personnel should be familiar with the occurrence of DCTs, particularly in the context of respiratory infections. General awareness of DCTs could not only circumvent misdiagnosis and needless pharmacotherapeutic regimes, it could also prevent utilization of costly resources such as infectious disease consultations. Without this familiarity, the presence of DCTs could easily be mistaken for disease with underlying infectious or inflammatory etiology.

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References

1. Moffitt C. (1994). Parasitic infections of the central nervous system. *Pediatric Annals.* 23: 424-433.
2. Schmidt GD and Roberts LS. (1989). The amebas. In: *Foundations of Parasitology, 4th ed.* Brake DK (ed). Times Mirror/Mosby College Publishing: St. Louis, pp. 110-112.
3. Rein MF. (1995). Trichomonas vaginalis. In: *Principles and Practice of Infectious Diseases, 4th ed.* Mandell G *et al.* (eds). Churchill-Livingstone, New York, pp. 2493-2496.
4. Adimora A, Hamilton H, Holmes K, *et al.* (1994). Trichomonas vaginalis and trichomoniasis. In: *Sexually Transmitted Diseases*, 2nd ed. Jeffers D and Melvin S (eds). McGraw-Hill Inc., New York, pp. 212-222.
5. Okamoto S, Wakui M, Kobayashi H, *et al.* (1998). Tritrichomonas foetus meningoencephalitis after allogeneic peripheral blood stem cell transplantation. *Bone Marrow Transplantation.* 21: 89-91.
6. Ashfaq-Drewett R, Allen C, and Harrison RL. (1990). Detached ciliary tufts: Comparison with intestinal protozoa and a review of the literature. American *Journal of Clinical Pathology.* 93: 541-545.
7. Kuritzkes D, Rein M, Horowitz S, *et al.* (1988). Detached ciliary tufts mistaken for peritoneal parasites: A warning. *Review of Infectious Diseases.* 10: 1044-1047.
8. Roxby CM, Wood M, Martin AM, et al. (1986). Ciliated organisms seen in fluid following dialysis. *Lancet.* 1: 916.
9. Mahoney CA, Sherwood N, Yap EH, *et al.* (1993). Ciliated cell remnants in peritoneal dialysis fluid. *Archives of Pathology and Laboratory Medicine.* 117: 211-213.
10. Hubel E, Kanitz M, and Kuhlmann U. (1990). Ciliocytophthoria in peritoneal dialysis effluent. *Peritoneal Dialysis International.* 10: 179-182.
11. Ash LR and Orihel TC. (1997). Fecal elements and cellular artifacts in stained fecal smears. In: *Atlas of Human Parasitology, 4th ed.* American Society of Clinical Pathologists, Chicago, pp. 370-371.
12. Hollander DH and Gupta PK. (1974). Detached ciliary tufts in cervico-vaginal smears. *Acta Cytologica.* 18: 367-369.
13. Naradzay JFX, Browne BJ, Rolnick MA, *et al.* (1999). Cerebral ventricular shunts. *Journal of Emergency Medicine.* 17: 311-322.
14. Sekhar LN, Moossy J, and Guthkelch AN. (1982). Malfunctioning ventriculoperitoneal shunts. *Journal of Neurosurgery.* 56: 411-416.
15. Kaufman BA and Park TS. (1999). Ventricular anatomy and shunt catheters. *Pediatric Neurosurgery.* 31: 1-6.
16. Pattisapu JV, Trumble ER, Taylor KR, et al. (1999). Percutaneous endoscopic recanalization of the catheter: A new technique of proximal shunt revision. *Neurosurgery.* 45: 1361-1367.
17. Sidawy MK, Chandra P, and Oertel YC. (1987). Detached ciliary tufts in female peritoneal washings. *Acta Cytologica.* 31: 841-844.

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A Perplexing Peripheral Neuropathy

Andrew S.-P. Lim, B.Sc. (OT3) and Warren Shih, B.Sc. (OT3)

Case Presentation

A 63-year-old woman presented to the emergency department in a wheelchair complaining of difficulty walking.

The patient first noticed symptoms of weakness three months before admission, first in her right leg and then in both. The weakness was mild and stable until six weeks prior to admission, at which time it began to get steadily worse. At this time, the patient also began noticing weakness in her hands. Before the onset of weakness, the patient was able to walk 3-4 miles a day. At the time of her presentation to the emergency department, she had difficulty with stairs, rising from a low chair, doing up buttons, and walking more than nine steps.

In addition to the sudden progression of her weakness, around six weeks prior to admission, the patient also started to notice intermittent brief paresthesiae in her upper and lower extremities including a "pins and needles" sensation in her fingers, chest, and back. She also felt a vague leg pain at rest that increased with walking. She noticed aching in her ankles and knees, but did not notice any swelling. She complained of cramping in her toes and a sensation of coldness in her feet.

Around the same time as her motor symptoms began, the patient also started to experience other problems. She complained of constipation, which started 10 weeks before admission and was ongoing. She also complained of fainting episodes, one of which led to a 911 call. When queried, she reported a dry mouth but not dry eyes. She complained of a general lack of energy.

Six weeks prior to the onset of her weakness, the patient experienced an episode of shingles which was successfully treated with acyclovir. The period immediately preceding the onset of her current symptoms also featured fluctuations in weight. Three months before the onset of her motor symptoms, the patient lost 20 lbs. However, she had since regained 18 lbs. She denied anorexia.

The patient suffers from hypothyroidism that is being treated with thyroxine. She also has a 10-year history of type II diabetes which is being managed with insulin. She has a history of hypertension and was taking ACE inhibitors. However, these were discontinued with the onset of the fainting spells.

Aside from those already noted, the patient had no other neurological symptoms. Specifically, she denied any numbness or tingling, sharp shooting pains, thoracic pain, back or neck pain, headaches, bladder urgency, dysphagia, postprandial fullness, diplopia or ptosis, change in hearing, or change in speech.

The patient denied any history of recent cough or hemoptysis, dyspnea, tuberculosis, pneumonia, pulmonary embolism, fever, or night sweats. She also denied any history of cardiac disease. Aside from her constipation, she denied any gastrointestinal symptoms including blood in the stool, diarrhea or abdominal pain. With regard to inflammatory disorders, she denied any history of autoimmune disease, swelling of the joints, arthralgia except for mild aching in the knees and ankles, rashes, history of Raynaud's phenomenon, photosensitivity, history of inflammatory arthropathy, or history of serositis. She had no history of trauma.

She had 2 live births 39 and 37 years ago, and had a hysterectomy 20 years ago. She has no drug or other allergies.

The patient lives at home with her husband and has no pets. She is retired but formerly worked as a cashier. She has no significant alcohol history but has a 30 pack-year history of smoking, having quit six months prior to admission. When queried, she reported no history of exposure to toxins or chemicals and had no recent history of foreign travel.

Both of the patient's parents were diabetic and both died of complications resulting from stroke.

On physical examination, the patient's blood pressure was 104/60 supine and 80/50 standing. Her heart rate was 84 bpm and regular. Her respiratory rate was 18 and her temperature was 36.8°C.

On inspection, there was no rash and no notable skin changes. Head and neck examination was normal. There was no cervical bruit and there were no abnormal heart sounds. The jugular venous pulse was normal. Peripheral pulses were present and there was no evidence of peripheral bruits or edema. The chest was clear and neither clubbing nor cyanosis was observed. The abdomen was soft, bowel sounds were present, and there was no evidence of ascites or organomegaly. There was no lymphadenopathy.

On neurologic examination, her mental status and speech were normal. Cranial nerves were intaet.

Inspeetion of the museles showed no faseieulations but did show wasting of the abduetor pollieis brevis and of the thenar eminenee of the left hand. A minimal deercase in bulk over the shins and the extensor digitorum brevis was also noted bilaterally. Tone was normal. Weakness in the upper and lower extremities was noted to be greater distally than proximally and was mildly asymmetrie. Deep tendon reflexes were absent globally and the patient had a left upgoing toe.

Sensory examination revealed normal perception of pinpriek, light touch, temperature, and position sense. The patient experienced no extinction to double simultaneous stimulation. The only sensory deficit was a mild decrease in the perception of vibration distally up to the ankle on the right side and up to the toes on the left side. Coordination was normal.

On walking, the patient showed a Trendelenburg gait, almost collapsing at the hips and knees with ambulation. The gait was wide based but was not spastic nor typically cerebellar.

CBC and differential were normal. PT, PTT, and ESR were normal. Electrolytes, BUN, and creatinine were normal as were GGT, alkaline phosphatase, ALT, AST, bilirubin, LDH and CK. Total serum proteins, serum albumin, and serum IgG levels were all slightly below normal at 59 g/L, 32 g/L, and 6.6 g/L, respectively. Other serum protein levels, ineluding α-1 globulins, α-2 globulins, ß-globulins and γ-globulins, complement C3, and complement C4 were normal. Cryoproteins were not detectable.

Endocrine and nutritional laboratory investigations showed an elevated random glucose at 15 mM, an elevated HbA1C at 0.096 and an elevated TSH at 7.97 mU/L. Levels of free T4, vitamin B12, and red blood eell folate were normal.

Urinalysis demonstrated elevated levels of ketones at 3.9 mmol and glucose at 55 mmol. There were oeeasional hyaline casts.

A rheumatology panel including ANA, SSA, SSB, SM, RNP, ANCA, and SLC was completely negative.

The patient had normal levels of the tumor markers alpha-fetoprotein, ß2-microglobulin, CA125, CA19.9, careinoembryonie antigen, and SSC. Levels of ß-human chorionic gonadotropin and CA15.3 were elevated on one occasion but were normal on subsequent retesting.

Serological tests showed no evidenee of *Treponema pallidum*, *Borrelia burgdorferi*, or hepatitis A, B, or C viruses.

The cerebrospinal fluid was of normal eolor and clarity. Levels of erythrocytes and leukoeytes were normal as was the leukoeyte differential eount. There was no oligoclonal banding and both the fractional IgG level and the IgG:albumin index were normal. However, the total level of IgG was elevated (148 mg/L, normal range 10-80 mg/L) as was the IgG synthesis rate (14.0 mg/day, normal <3.4 mg/day). CSF glueose was elevated (5.8 mM, normal range 2.2-3.9 mM) and the CSF protein level was markedly elevated (1841 mg/L, normal range 140-520 mg/L).

Cerebrospinal fluid eulture showed no growth after 5 days and CSF eytology showed no polymorphs, no mieroorganisms, no malignant eells, but oeeasional mononuelcated white blood eells.

An ECG revealed no abnormalities exeept for a mild left axis deviation.

A ehest X-ray showed a mild apical pleural thiekening, but was otherwise normal. A ehest CT showed a 5 mm foeal nodular opacity in the apieal segment of the right upper lobe. An abdominal CT revealed three small well-eireumseribed cystic lesions in the liver, the largest of whieh was 1 cm in diameter. These were interpreted as simple cysts. There was no evidenee of intra-abdominal soft tissue masses or adenopathy. Abdominal and pelvic ultrasounds eonfirmed the findings on CT and showed no additional pathology. An MRI of the lumbar, thoracic and cervical regions revealed a mild left posterolateral disc protrusion L4-5 with an annular tear. However, this did not impinge on neural structures. The brain MRI was normal. A skeletal survey revealed no osseous lesions.

Nerve conduction studies showed a marked decrease in the amplitude of sensory nerve action potentials (SNAPs). SNAPs were unobtainable in the right median nerve, right sural nerve, and right superficial peroneal nerve and were decreased in the ulnar nerve bilaterally and the superficial radial nerve bilaterally. Nerve conduction studies also showed a decrease in the amplitude of eompound muscle action potentials (CMAPs) in the ulnar, median, posterior tibial, and peroneal nerves bilaterally but not in other nerves. However, they did not show evidence of conduction block or signifieant slowing of motor conduction veloeities.

Needle electromyography revealed some mild active denervation with 1+ positive sharp waves and fibrillation potentials in the extensor hallueis longus bilaterally and the right T3 paraspinal museles. It also revealed mild to moderate chronic neurogenie ehanges of slightly complex, occasionally unstable motor unit potentials (MUPs) in the right tibialis anterior, medial gastrocnemius, iliopsoas, and glutcus maximus museles.

Discussion of Clinical Findings

In any case involving weakness, the first task is to differentiate between myogenie and neurogenic causes. In this case, there are a few reasons to suspect a neurogenie rather than a myogenie eause. A distal distribution of weakness, as observed in this ease, is more commonly seen in neurogenic rather than myogenic disorders. However, more importantly, the triad of distal weakness, sensory symptoms (both positive and negative in this ease), and autonomic dysfunetion (eonstipation, dry mouth, and postural hypotension in this case) is strongly suggestive of a neuropathy rather than a myopathy. Furthermore, the absenee of eentral signs, sueh as diffieulties with cognition, memory, and language and the distal distribution of symptoms, is charaeteristie of peripheral neuropathy.

There are three categories of peripheral neuropathy: polyneuropathy, mononeuritis multiplex, and neuronopathy. Polyneuropathy is characterized by a nearly symmetrie presentation that is of a distal "stocking-glove" distribution. Mononeuritis multiplex is characterized by the sequential

involvement of different peripheral nerves resulting in an asymmetric onset and a patchy distribution of symptoms. However, later on, these patches of symptoms will begin to overlap and will summate to form a "stocking-glove" symmetrical distribution of symptoms.[1] Neuronopathy, which affects the cell bodies of peripheral nerves, is characterized by a predominantly proximal distribution of symptoms. This case is consistent with both a polyneuropathy and a mononeuritis multiplex.

The differential diagnosis of mononeuritis multiplex includes inflammatory conditions such as sarcoidosis and vasculitis, metabolic abnormalities such as diabetes and cryoglobulinemia, infections such as leprosy, and neoplasia. Meanwhile, the differential diagnosis of a polyneuropathy can be divided into acute, sub-acute, and chronic causes. Acute polyneuropathies can be caused by Guillain-Barré syndrome, arsenic poisoning, toxins, porphyria, and critical illness. Sub-acute and chronic polyneuropathies can be caused by exposure to toxins, nutritional deficiency, metabolic causes such as diabetes, hypothyroidism, uremia, infections such as Lyme disease[2], and plasma cell disorders such as multiple myeloma, Waldenstrom's macroglobulinemia, and primary amyloidosis. There is also a chronic inflammatory demyelinating polyneuropathy (CIDP), many hereditary polyneuropathies, and a series of polyneuropathies associated with paraproteinemias. The time course of the symptoms rules out acute polyneuropathy.

Table 1
Differential Diagnosis for Mononeuritis Multiplex

Inflammatory
Sarcoidosis
Vasculitis
Metabolic
Diabetes mellitus
Cryoglobulinemia
Other
Infections (e.g., *M. leprae*)
Neoplastic

Some of the other conditions in the differential diagnoses of mononeuritis multiplex and polyneuropathy can be ruled out as well. The possible infectious causes can be ruled out by a lack of accompanying symptoms (such as fever, skin lesions etc.), a lack of an exposure history, and negative serology. Hereditary causes, except for familial amyloidosis, can be ruled out by the late onset and the non-uniform distribution of symptoms seen in this patient. Toxic and nutritional neuropathies can be ruled out by the lack of an appropriate exposure history and the lack of supportive laboratory results. Sarcoidosis can also be eliminated from the differential diagnosis due to a lack of associated symptoms such as hilar lymphadenopathy, pulmonary infiltration, and skin or eye lesions.[3] Uremic neuropathy can be ruled out since it is usually only associated with severe renal dysfunction, while this patient's laboratory results indicated normal or near normal renal function. Paraproteinemic causes of neuropathy can be ruled out by the absence of detectable paraproteins on serum electrophoresis. However, non-secreting or poorly secreting plasma cell disorders will be discussed later.

The remaining conditions are chronic inflammatory demyelinating neuropathy, diabetic neuropathy, hypothyroid neuropathy, cryoglobinemic neuropathy, neuropathy secondary to plasma cell disorders, neuropathy secondary to familial amyloidosis, paraneoplastic polyneuropathy, and vasculitic neuropathy.

Before one considers each of these in turn, it is useful to consider the significance of some of the laboratory findings in the present case. The first finding to consider is the elevated CSF protein level. The CSF protein in this patient is so high that it can be explained by only a handful of conditions. Unfortunately, one of these conditions is diabetes mellitus, from which this patient is known to suffer. Diabetic patients can have CSF protein levels as high as 5000 mg/L even in the absence of any peripheral neuropathy.[1] Thus, the use of CSF protein levels to differentiate between the various potential causes of peripheral neuropathy may not be as fruitful in this patient as in others.

The other results to consider are those found in nerve conduction studies (NCS) and electromyography (EMG). NCS and EMG are among the most important laboratory investigations for peripheral neuropathy. They have three main uses in the investigation of peripheral neuropathy. The first is to differentiate between axonopathies and demyelinating disorders, the second is to identify subclinical abnormalities and the third is to identify subtle asymmetries in the distribution of symptoms.

Axonopathies are characterized by decreased amplitudes and normal or near normal conduction velocities on NCS.[1] They are also characterized by evidence of denervation on EMG.[1] Signs of active denervation include fibrillation potentials, positive sharp wave potentials, and a decreased interference pattern while signs of chronic denervation include both increased duration and complexity of MUPs. Meanwhile, demyelinating disorders are characterized by markedly decreased conduction velocities and occasionally by dispersion of compound action potentials. In this case, the results of NCS and EMG clearly support an axonopathy — SNAP's and CMAP's had markedly decreased amplitudes while nerve conduction velocities were barely affected.

With regard to subclinical abnormalities, EMG studies were able to identify denervative changes in some paraspinal muscles suggesting a radicular involvement not evident on clinical examination.

Based on these electrodiagnostic results, it is possible to rule out one of the most common causes of peripheral neuropathy – chronic inflammatory demyelinating disorder (CIDP). CIDP almost invariably shows demyelinating characteristics on NCS/EMG while this patient's studies revealed a predominantly axonal disorder.

Because this patient is known to suffer from poorly controlled diabetes, one of the most important remaining conditions to consider is diabetic neuropathy. Several aspects of this case are consistent with diabetic neuropathy. Clinically, diabetic neu-

ropathy has been associated with postural hypotension[1] and constipation is the most common gastrointestinal symptom in diabetic neuropathy.[1] Also, diabetic neuropathy is frequently associated with areflexia in the distribution of the affected nerves.[1] With regard to the results of NCS and EMG, diabetic neuropathy is associated with decreased amplitudes with near normal conduction velocities and results in denervative changes on EMG.[4] While the diabetic neuropathy accounts nicely for the patient's autonomic symptoms and is consistent with her poorly controlled diabetes, it cannot account for many of the remaining symptoms. For example, the distal weakness is not a typical symptom of diabetic neuropathy, which typically features predominantly proximal weakness.[5]

Although hypothyroidism produces a neuropathy with NCS and EMG features similar to that observed in this patient,[6] several aspects argue against hypothyroidism as the primary cause of this patient's neuropathy. Hypothyroid neuropathy is characterized by a sensory loss followed by weakness rather than the other way around.[1] Also, hypothyroid neuropathy features a loss of touch, vibration, and position sense in almost all instances whereas in this case, only vibration sense was lost.[1] Finally, hypothyroid neuropathy is generally mild and is typically associated with a more severe hypothyroidism than was seen in this case.[7]

Cryoglobulinemia is associated with peripheral neuropathy. However, cryoglobulinemia does not usually manifest itself as an isolated peripheral neuropathy. Rather, it usually presents as some combination of Raynaud's phenomenon, purpura, urticaria, arthralgia, and renal disease.[10] Also, laboratory tests for cryoglobulins in this patient were negative.

Peripheral neuropathies have been associated with various plasma cell disorders. These include primary amyloidosis, multiple myeloma, and Waldenstrom's macroglobulinemia.

Primary amyloidosis results from fibril formation by monoclonal antibody light chains[11] and can be associated with a sensorimotor peripheral neuropathy. The peripheral neuropathy of primary amyloidosis is associated with an increased CSF protein level and an increased CSF IgG fraction. Furthermore, it typically yields NCS/EMG results consistent with axonopathy. Both are consistent with the results seen in the present patient. However, unlike the situation seen in this patient, the peripheral neuropathy associated with primary amyloidosis is predominantly sensory in nature.[12] Furthermore, primary amyloidosis is strongly associated with abnormal serum and urine protein electrophoresis[1] and usually features systemic signs and symptoms including cardiomyopathy, hepatomegaly, and splenomegaly,[12] none of which were observed.

Multiple myeloma represents a malignant proliferation of plasma cells derived from a single clone.[13] The most common symptoms are bone pain, susceptibility to bacterial infections, and renal failure.[13] Serum or urine electrophoresis usually reveals the presence of a monoclonal paraprotein band[14] and a radiologic bone survey will often reveal bony lesions. These lesions may be of two types: osteolytic or osteosclerotic.

The peripheral neuropathy associated with osteolytic multiple myeloma is a sensorimotor one.[1] It is heralded by numbness and tingling in the feet accompanied by a slight weakness and frequently antedates the discovery of the underlying malignancy. Typically, all sensory modalities will be impaired and autonomic involvement does not occur.[1] Pain is a common feature. Laboratory tests typically reveal an elevated CSF protein level and axonopathic changes on NCS/EMG.

The peripheral neuropathy associated with osteosclerotic multiple myeloma is similar to that of osteolytic multiple myeloma but differs in several respects. As with osteolytic myeloma, the peripheral neuropathy of osteosclerotic myeloma is a sensorimotor type that often antedates the diagnosis.[1] However, pain is not a common feature and sensory loss affects mainly large fibre modalities, leaving pain and temperature sensation intact. CSF protein levels[1] and NCS/EMG results[15] are similar to osteolytic myeloma. Unlike osteolytic myeloma, levels of paraprotein in osteosclerotic myeloma are low.[9] Furthermore, in osteosclerotic myeloma, there is a lower incidence of anemia, hypercalcemia, chronic renal failure, fatigue and bone pain.

A form of myeloma may be contributing to this patient's symptoms. The observed peripheral neuropathy resembles closely that of osteosclerotic myeloma except for the presence of autonomic involvement, which may be accounted for by a diabetic neuropathy. Meanwhile, the presence of a positive IgG synthesis rate in the CSF points to the possibility of a plasma cell tumour somewhere in the CNS. The inability to detect elevated serum paraproteins, while at odds with a diagnosis of osteolytic myeloma, is consistent with the low serum paraprotein levels associated with osteosclerotic myeloma. Arguing against myeloma are a negative bone survey, absence of bone pain, absence of hypercalcemia, a normal serum IgG, and negative tests for tumour markers. However, these signs and symptoms are often absent in early myeloma.

Table 2
Differential Diagnosis for Polyneuropathy[31]

Acute Disease (Days to Weeks)	
Demyelinating	Axonal
Guillain-Barré syndrome	Toxin-induced neuropathy
Arsenical polyneuropathy	Porphyria
	Critical-illness polyneuropathy
	Axonal Guillain-Barré syndrome

Waldenstrom's macroglobulinemia is a malignancy of lymphoplasmacytoid cells secreting IgM.[13] Like osteolytic myeloma, it is associated with the presence of a serum paraprotein. Unlike myeloma, it is not associated with bony lesions or with renal dysfunction. Waldenstrom's macroglobulinemia is almost always associated with a normocytic, normochromic anemia.[13] While Waldenstrom's macroglobulinemia is often associated with a peripheral neuropathy, there are several lines of argument against this as a contributing factor to the present patient's symptoms. Chief among these are the lack of anemia and the lack of a serum paraprotein, both of which are almost always observed in Waldenstrom's macroglobulinemia, unlike with osteosclerotic myeloma. Furthermore, this patient lacked both hepatosplenomegaly and lymphadenopathy and tested negative for a panel of tumour markers.

neuropathies as a result of plasma cell neoplasia have been discussed. However, plasma cell disorders are not the only neoplasias associated with peripheral neuropathy. Paraneoplastic sensorimotor neuropathies have been reported with several other types of tumours, including squamous cell lung carcinoma, breast, and stomach, as well as with hematologic malignancies such as Hodgkin's disease, and lymphoma.[16] The neurologic symptoms of paraneoplastic sensorimotor neuropathy including muscle wasting and weakness and distal limb paresthesias,[16] match very closely with those observed in the present patient. Moreover, the neuropathy is typically axonal in nature.[16]

Of all the causes of mononeuritis multiplex, by far the most common are the vasculitides. Although there are a great multitude of vasculitis syndromes, their associated peripheral neuropathies share a common underlying pathophysiology – inflammation and occlusion of the vasa nervosa, nerve ischemia, and axonal degeneration with or without secondary demyelination. Vasculitic peripheral neuropathy typically distributes as a mononeuritis multiplex that then coalesces into a symmetric, predominantly distal polyneuropathy affecting the arms as well as the legs.[1] However, over one-third of vasculitic peripheral neuropathies display a distal symmetric pattern from the outset.[17]

Many of the vasculitis syndromes feature prominent systemic signs and symptoms that are used to classify them. Polyarteritis nodosa (PAN) typically involves the renal and visceral arteries[18] and peripheral neuropathy occurs subsequent to other manifestations of generalized disease, such as fever, pericarditis, renal failure or abdominal pain.[1] That none of these were present in this patient makes PAN an unlikely cause of her neuropathy. Furthermore, the ESR is almost always elevated in PAN[19] while it was normal in this patient.

A vasculitic peripheral neuropathy is sometimes associated with chronic rheumatoid arthritis (RA). However, as with PAN, the vasculitis of RA is almost invariably systemic. While this patient did complain of some arthralgia, she did not have a history of chronic arthritis, did not complain of systemic vasculitic symptoms, and showed negative results on a rheumatology panel.

Systemic lupus erythromatosus (SLE) can be accompanied by a peripheral neuropathy similar to that seen in this patient. Signs of SLE include arthritis, serositis, renal failure, oral ulcers, photosensitivity, and a malar rash,[20] none of which this patient possessed. Laboratory testing of patients with SLE typically reveals the presence of anti-nuclear antibodies and anti-Sm antibodies. This patient lacked both.

Similar to the syndromes of polyarteritis nodosa, rheumatoid arthritis, and systemic lupus erythromatosus discussed above, this patient also lacked the characteristic symptoms and signs of most of the other vasculitis syndromes. These include Sjogren's syndrome (SSA, SSB, keratoconjunctivitis sicca, xerostomia, and arthritis[1]), Churg-Strauss syndrome (eosinophilia, asthma, sinusitis or rhinitis[21]), scleroderma (Raynaud's phenomenon and cutaneous changes), Wegener's granulomatosis (upper and lower airway symptoms, skin lesions, renal disease, ANCAs, and eye involvement)[18], and mixed connective tissue disease (lymphadenopathy, anti-Smith, and anti-RNP).[9]

There are two reported vasculitis syndromes that lack prominent systemic signs. Both result in a peripheral neuropathy resembling that seen in this patient and, while rare, may account for her symptoms. They are microvasculitis as a remote effect of carcinoma,[22] and idiopathic nonsystemic vasculitic neuropathy.[23,24]

In at least three reported cases of microvasculitis as a remote effect of carcinoma,[22] patients presented with a mononeuritis multiplex weeks to months prior to the diagnosis of a malignancy. In two of the cases, this diagnosis of clinically unrecognized carcinoma was made post-mortem. As with the current patient, the observed peripheral neuropathy was predominantly distal with asymmetrical electrodiagnostic findings. Furthermore, as with this patient, the vasculitis was limited mainly to the peripheral nervous system.

A study of 20 patients with idiopathic nonsystemic vasculitic neuropathy was reported by Dyck and colleagues in 1987.[24] The findings in the present case bear a striking resemblance to those described in this report. Clinically, the findings described by Dyck and colleagues included muscle weakness and atrophy, paresthesiae, pain, and sensory deficits, with few systemic symptoms or serologic abnormalities. The distribution of these findings was reported to be that of a mononeuritis multiplex in 60% of patients and a distal sensorimotor polyneuropathy in a further 15%. Laboratory testing revealed normal hematological and urological indices, normal ESRs, a normal CSF cellular content, a moderately elevated protein content, and absent ANA, rheumatoid factor, and cryoglobulin in the majority of the patients in the study. All these findings are mirrored in our patient.

In summary, given the paucity of systemic findings and the electrodiagnostic findings indicating an axonal rather than demyelinating disorder, one is able to rule out a great many of the conditions in the differential diagnosis of polyneuropathy and mononeuritis multiplex. The remaining conditions include diabetic neuropathy, osteosclerotic myeloma, microvasculitic neuropathy associated with occult neoplasm, nonvasculitic paraneoplastic neuropathy, and idiopathic nonsystemic vasculitic neuropathy. Given that this patient had poorly controlled diabetes mellitus, it seems likely that diabetic neuropathy may have contributed to at least some of her symptoms. However, it is unlikely to account for all of this patient's symptoms. Thus, the clinical diagnosis may best be described as a paraneoplastic or vasculitic neuropathy against a background of diabetic neuropathy.

Clinical Differential Diagnosis

? osteosclerotic myeloma
? microvasculitic neuropathy secondary to occult neoplasm
? nonvasculitic paraneoplastic neuropathy
? idiopathic vasculitic neuropathy
? diabetic neuropathy

Pathological Findings

Biopsies of the left sural nerve and left gastrocnemius muscle were performed.

Light microscopic examination of frozen gastrocnemius muscle sections showed an increased variability in fibre size and shape; on ATPase staining, this was shown to be attributable to type II muscle fibre atrophy of moderate severity with a geographic distribution. Examination of both frozen and paraffin-embed-

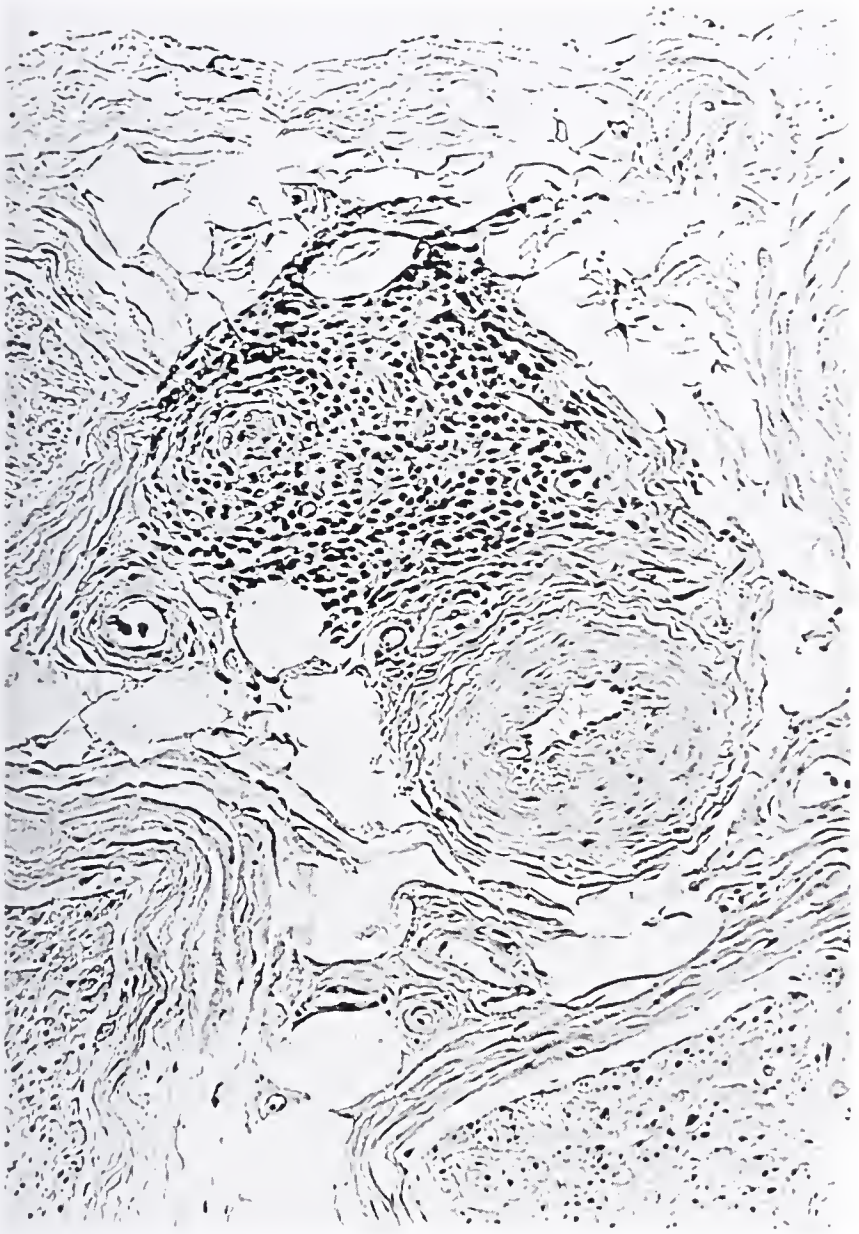

Figure 1a.

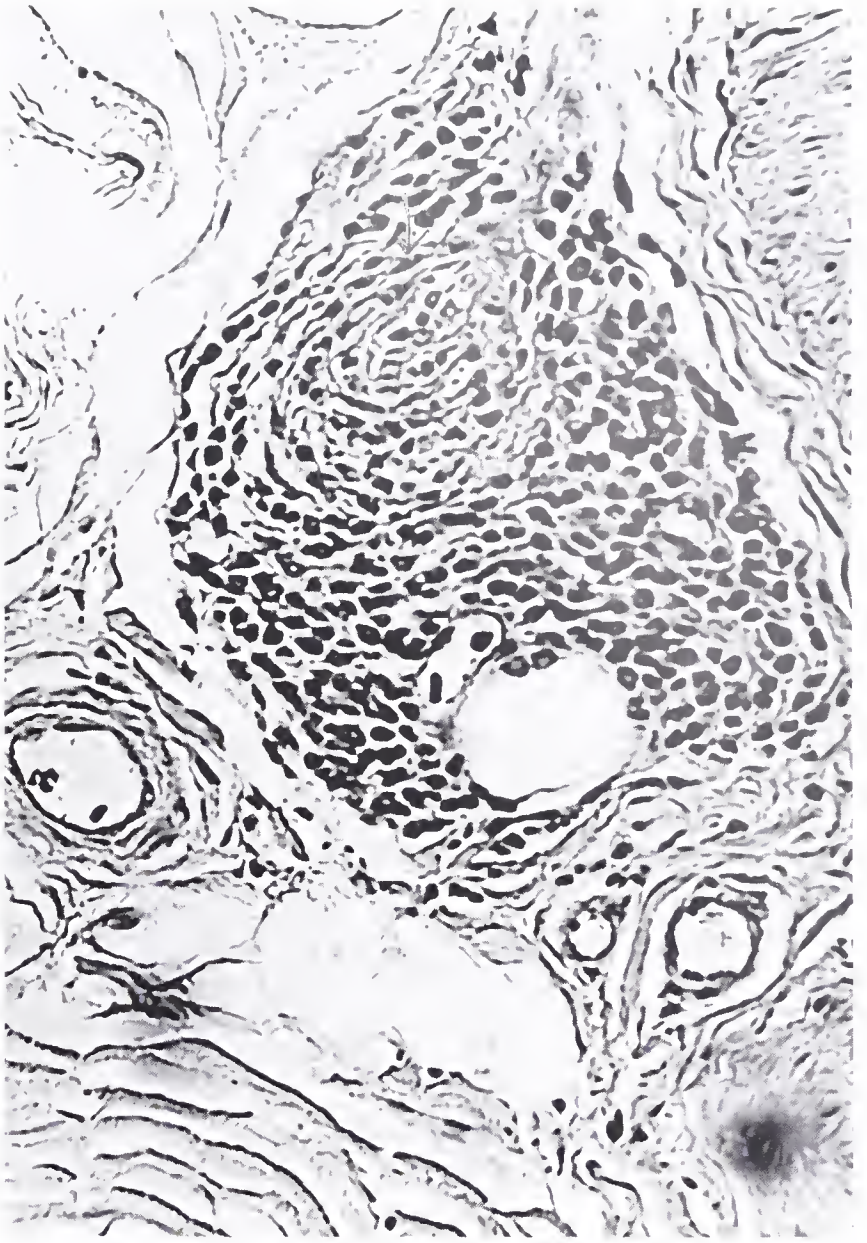

Figure 1b.

ded sections revealed a moderate endomysial lymphocytic infiltrate. Perivascular inflammatory foci were also noted. Rimmed vacuoles or intracellular inclusions were not seen.

Examination of paraffin-embedded sural nerve sections showed intense epineurial lymphocytic infiltrates affecting the walls of small calibre vessels as well as focal evidence of fibrinoid necrosis (Figures 1a and 1b). Examination of epon-embedded sections of sural nerve showed a decrease in the population of both large and small myelinated fibres, especially small ones. Some "onion-bulb" formations were noted and some large fibres displayed abnormally thin myelin sheets. Endoneurial vessels showed hyalinization of vessel walls and occasional "onion skinning".

Discussion of Pathological Findings

The differential diagnosis for moderate selective atrophy of type II fibres includes neurogenic atrophy, disuse atrophy, and steroid therapy. Because this patient has no history of steroid therapy, this could not be the cause. Given this patient's history and the geographic distribution of the atrophy, the observed atrophy was probably neurogenic.

Meanwhile, the endomysial lymphocytic infiltrate and perivascular inflammatory foci are indicative of inflammatory myopathy. That this myopathy is mild is highlighted by the low CK levels observed in this patient. However, despite the subclinical presentation of the myositis, it is useful to consider the differential diagnosis of inflammatory myopathy because some of the etiologies of myositis are treatable. The differential diagnosis of inflammatory myopathy for a patient such as this includes idiopathic polymyositis, idiopathic dermatomyositis, inclusion body myositis, myositis associated with malignant disease, myositis associated with vasculitic disease, drug-induced myositis, and infective myositis.[25] Of these, idiopathic dermatomyositis, inclusion body myositis, infective myositis, and drug induced myositis are easily ruled out, due to a lack of accompanying symptoms.

It is possible that vasculitis-associated myositis, paraneoplastic myositis, or idiopathic polymyositis might have contributed to the patient's symptoms. While the patient's main symptoms (distal weakness, sensory loss, and paresthesiae) cannot be explained by myositis alone, it is possible that one of these three forms of myositis may have contributed somewhat to her weakness.

The other pathological findings in the sural nerve are for the most part fairly nonspecific. The decrease in the population of myelinated fibres is a nonspecific sign of peripheral neuropathy involving either primary or secondary axonal degeneration and would be expected in any of the conditions noted in the clini-

The apparent preferential involvement of small fibres may support a role for diabetes in the neuropathy because diabetic neuropathy has been associated with disproportionate involvement of such fibres.[26]

The description of "onion-bulb" formations denotes the concentric rings of Schwann cell nuclei surrounding a nerve fibre that result from repeated demyelination and remyelination. Such formations have been associated with both paraneoplastic neuropathy[27] and diabetic neuropathy,[28] among others.

The description "onion-skinning" refers to intimal thickening caused by the concentric proliferation of smooth muscle cells and the deposition of collagen. Both onion-skinning and hyalinization are associated with diabetes mellitus.[29,30] They have also been observed in nonsystemic vasculitic neuropathy as a remote effect of cancer.[22]

In summary, it is clear from the microscopic examination that there is an ongoing vasculitic process. The only two neuropathic vasculitides that are consistent with the clinical picture and laboratory findings are idiopathic nonsystemic vasculitic neuropathy and paraneoplastic vasculitic neuropathy. Because of the relative rarity of idiopathic nonsystemic vasculitic neuropathy as compared to paraneoplastic vasculitic neuropathy, the likely diagnosis is a vasculitic neuropathy as a remote effect of an occult neoplasm. The presence of an occult neoplasm would also better account for the inflammatory myopathy, the pathological vascular changes, and may account for the high CSF IgG levels. Given that the patient has poorly controlled diabetes, the paraneoplastic vasculitic neuropathy is likely accompanied by a diabetic neuropathy that may account for some of the autonomic symptoms and some of the characteristic pathologic features discussed above.

Pathological Diagnosis

Vasculitic neuropathy secondary to occult neoplasm
Diabetic neuropathy

Epilogue

In cases of paraneoplastic vasculitic neuropathy, the recommended course of action is to treat the underlying malignancy. If this is not possible, then the recommended course is a combination of prednisolone and an immunosuppressant such as cyclophosphamide.[18]

Meanwhile, diabetic neuropathy is best treated by managing blood glucose levels.

On discharge 29 days after admission, this patient was prescribed azathioprine 100 mg per day and prednisone 60 mg per day for 30 days to control the vasculitis. To combat the calcium leeching effects of prednisone, she was prescribed 400 U of vitamin D per day as well as 500 mg of $CaCO_3$ three times a day. To control her hypothyroidism, she was prescribed L-thyroxine 125 µg per day, and to control her blood glucose, she was prescribed an insulin regimen consisting of both NPH and regular insulin. She is currently undergoing follow up for her lung nodule and a continued workup for suspected malignancy.

Acknowledgements

The authors would like to thank Dr. A.J. Stoessl of the Division of Neurology and Dr. J.A. Maguire of the Department of Pathology, both of the Vancouver Hospital and Health Sciences Centre, for providing the case for this report as well as for providing helpful guidance throughout.

References

1. Schaumburg HH, Berger AR, and Thomas PK. (1992). Disorders of Peripheral Nerves, 2nd ed. F.A. Davis Company: Philadelphia.
2. Steere AC. (1982). Lyme disease. *N Eng J Med.* 321: 586-596.
3. Siltzbach LE, James DG, and Neiville E. (1974). Course and prognosis of sarcoidosis around the world. *Am J Med.* 57: 847-52.
4. Dyck PJ, Karnes JL, Daube J, *et al.* (1985). Clinical and neuropathological criteria for the diagnosis and staging of diabetic polyneuropathy. *Brain.* 108: 861-80.
5. Asbury, AK. (1998). Diseases of the Peripheral Nervous System. In: *Harrison's Principles of Internal Medicine, 14th ed.* Fauci AS *et al.* (eds). McGraw-Hill: New York, pp. 2457-2469.
6. Dyck PJ, and Lambert EH. (1970). Polyneuropathy associated with hypothyroidism. *J Neuropathol Exp Neurol.* 29: 631-58.
7. Grabow JD and Chou SM. (1968). Thyrotropin hormone deficiency with a peripheral neuropathy. *Arch Neurol.* 19: 284-91.
8. Kelly JJ Jr, Kyle RA, O'Brien PC, and Dyck PJ. (1981). Prevalence of monoclonal protein in peripheral neuropathy. *Neurology.* 31: 1480-3.
9. Goetz CG, and Pappert EJ. (1999). *Textbook of Clinical Neurology.* W.B. Saunders: Philadelphia.
10. McLeod JG, Walsh JC, and Pollard JD. (1984). Neuropathies associated with paraproteinemias and dysproteinemias. In: *Peripheral Neuropathy. 2nd ed.* Dyck PJ *et al.* (eds). W.B. Saunders: Philadelphia, pp. 1847-65.
11. Sipe JD, and Cohen AS. (1998). Amyloidosis. In: *Harrison's Principles of Internal Medicine, 14th ed.* Fauci AS *et al.* (eds). McGraw-Hill: New York, pp. 1856-1860.
12. Dayan AD, Urich H, and Garner-Thorpe C. (1971). Peripheral neuropathy and myeloma. *J Neurol Sci.* 14: 21-35.
13. Longo, DL. (1998). Plasma Cell Disorders. In: *Harrison's Principles of Internal Medicine, 14th ed.* Fauci AS *et al.* (eds). McGraw-Hill: New York, pp. 712-718.
14. Kelly JJ Jr., Kyle RA, and Larov N. (1987). *Polyneuropathies associated with plasma cell dyscrasias.* Martinus Nijhoff Publishing: Boston.
15. Ohi T, Nukada H, Hyle RA, and Dyck PJ. (1983). Detection of an axonal abnormality in myeloma neuropathy. *Ann Neurol.* 14: 120. Abstract.
16. Brown, RH Jr. (1998). Paraneoplastic Neurologic Syndromes. In: *Harrison's Principles of Internal Medicine, 14th ed.* Fauci AS *et al.* (eds). McGraw-Hill: New York, pp. 622-627.
17. Said G, Lacroix-Ciaudo C, Fujimura H, *et al.* (1988). The peripheral neuropathy of necrotizing arteritis: a clinicopathological study. *Ann Neurol.* 23: 461-65.
18. Fauci, AS. The Vasculitis Syndromes. In: *Harrison's Principles of Internal Medicine, 14th ed.* Fauci AS *et al.* (eds). McGraw-Hill: New York, pp. 1910-1922.
19. Hawke SH, Davies L, Pamphlett R, *et al.* (1991). Vasculitic neuropathy. A clinical and pathological study. *Brain.* 114: 2200-2202.
20. Gladman DD, and Urowitz MB. (1997). Clinical and Laboratory Features. In: *Primer on the Rheumatic Diseases, 11th ed.* Klippel JH (ed). Arthritis Foundation: Atlanta, pp. 251-257.
21. Churg J, and Strauss L. (1951). Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am J Pathol.* 27: 277-301.
22. Johnson PC, Rolack LA, Hamilton RH, and Laguna JF. (1979). Paraneoplastic vasculitis of nerve: a remote effect of cancer. *Ann Neurol.* 5: 437-444.
23. Kissell JT, Slivka AP, Warmoltz JR, *et al.* (1985). The clinical spectrum of necrotizing angiopathy of the peripheral nervous system. *Ann Neurol.* 18:251-57.
24. Dyck PJ, Benstead TJ, Conn DL, *et al.* (1987). Nonsystemic vasculitic neuropathy. *Brain.* 110: 843-53.
25. Lindsay KW, Bone I. (1997). Neurology and Neurosurgery Illustrated. Churchill Livingstone: Toronto.
26. Said G, Slama G, and Selva J. (1983). Progressive centripetal degeneration of axons in small fibre diabetic polyneuropathy. A clinical and pathological study. *Brain.* 106: 791-807.
27. Croft PB, Urich H, and Wilkinson M. (1967). Peripheral neuropathy of sensorimotor type associated with malignant disease. *Brain.* 90: 31-66.
28. Ballin RHM, and Thomas PK. (1968). Hypertrophic changes in diabetic neuropathy. *Acta Neuropathol (Berl).* 11: 93-102.
29. Fagerberg S-E. (1959). Diabetic neuropathy: A clinical and histological study on the significance of vascular affections. *Acta Med Scand.* 164 (suppl 345).
30. Timperley WR, Ward JD, Preston FG, *et al.* (1976). A reassessment of vascular factors in relation to intravascular coagulation. *Diabetologia.* 12: 237-43.
31. Case Records of the Massachusetts General Hospital. (1993) Case 21 - 1993. *N Eng J Med.* 328: 1550-58.

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In the Literature

Philippe L. Bedard, B.ArtsSc. (0T3)

This section of News and Views will present updates of recent advances in the medical and scientific literature.

Early Success of First Permanent Implant of Jarvik 2000 Heart

The use of permanent mechanical pump devices to improve circulatory function in patients with end-stage heart failure has been limited by the size of the devices, the reliance on hospital care for device maintenance, and the life-threatening complications of thromboembolism and infection. In the September 9th issue of *The Lancet*, Westaby and colleagues report on the first permanent implant of the Jarvik 2000 Heart into a 61 year-old man with symptomatic dilated cardiomyopathy, as part of a non-randomised, prospective assessment of the device in patients who are ineligible for cardiac transplantation. The thumb-sized pump was implanted into the apex of the patient's failing left ventricle through a thoracotomy and a tiny vascular graft was constructed to convey blood from the device to the patient's descending aorta. The power cable of the device was passed through the patient's chest and neck to a mounted pedestal behind his mastoid process. This pedestal is connected to an external battery and controller worn on the patient's belt. The single dial controller allows the patient to regulate the device's pumping efficiency according to activity level. Six weeks after implantation, the patient's left ventricular ejection fraction improved from less than 10% at baseline to 30%. His exercise tolerance increased and was accompanied by a decrease in bodyweight and disappearance of peripheral edema and ascites. There was no evidence of significant hemolysis or device-related complications, such as thromboembolism or infection. Although it is too early to draw definitive conclusions regarding the long-term safety and efficacy of the Jarvik 2000 Heart, the authors suggest that this initial intervention provides encouraging evidence for the therapeutic use of permanent mechanical circulatory support in patients with end-stage heart failure.

Westaby S, Banning AP, Jarvik R, *et al.* (2000). *Lancet.* 356: 900-903.

New Protein Linked to Alzheimer's Disease

Alzheimer's disease is characterized by the accumulation of amyloid-α (Aα) peptide in the brain that leads to the formation of neurotoxic plaques. Aα is generated from a larger transmembrane precursor, α-amyloid precursor protein (αAPP), through enzymatic cleavage by a complex of proteins that includes presinilin (PS1) and presinilin 2 (PS2). Missense mutations in PS1 and PS2 have been linked with familial Alzheimer's disease. To date, the search for other proteins involved in the formation of Aα has been unsuccessful. In the September 7th issue of *Nature*, Yu and colleagues report the discovery of a new transmembrane protein, nicastrin, which is involved in the processing of αAPP. Nicastrin was isolated from cultured cells overexpressing PS1 by immunoprecipitation with antibodies against PS1. The full-length cDNA for nicastrin was cloned and the gene for nicastrin maps to a region of chromosome 1 that has previously been associated with Alzheimer's disease. Further immunoprecipitation experiments with anti-nicastrin antibodies demonstrated that nicastrin interacts with PS1, PS2, and the extracellular portion of αAPP. Mutations that altered these interactions either increased or decreased the proteolytic cleavage of αAPP to yield Aα. Interestingly, experiments in the nematode, *C. elegans*, which knocked out the function of nicastrin yielded offspring with the same phenotype as those in which the Notch-signalling pathway was reduced. Notch is an important transcription factor released from a transmembrane precursor during development to upregulate the expression of genes involved in cell-fate determination. This finding suggests that nicastrin may be involved in a more broadly functioning proteolytic complex of proteins that process transmembrane proteins like αAPP and Notch. The authors speculate that nicastrin may also be a target for therapeutic manipulation in patients with Alzheimer's since it is involved in regulating the production of Aα.

Yu G, Nishimure M, Arawaka S, *et al.* (2000). *Nature.* 407:48-54.

Ondansetron Reduces Drinking among Biologically Predisposed Patients

Early-onset alcoholism is associated with patients who develop alcoholic behavior before the age of 25 and who demonstrate a broad range of anti-social behaviors.

Prior research has linked early-onset alcoholism with dysfunctional handling of the neurotransmitter serotonin in the brain. Selective serotonin (5-HT_3) receptors are known to be involved in mediating the euphoric effects of alcohol consumption by modulating the brain's dopamine reward system. Johnson and colleagues hypothesized that early-onset alcoholics would experience better drinking outcomes when treated with ondansetron, a 5-HT_3 antagonist frequently prescribed as an anti-nausea medication, when compared with late-onset alcoholics treated with a similar course of ondansetron. 321 patients diagnosed with alcoholism according to DSM-IIIR criteria were randomized in a double-blind study to receive either placebo or ondansetron. Patients were followed on a weekly basis and were asked to self-report their alcohol consumption and the number of days during which they had abstained from alcohol. Patients were also evaluated for plasma carbohydrate deficient transferrin (CDT) levels, an objective biological marker of their alcohol consumption. Early-onset alcoholics receiving ondansetron self-reported significantly lower numbers of drinks per day compared with placebo. Moreover, the mean log CDT ratio was significantly reduced in the ondansetron group. In con-

trast, there were no statistically significant findings achieved with the late-onset alcoholics receiving ondansetron when compared with placebo. These results support the theory of a biological basis for alcoholism and propose a targeted pharmacological therapy for a specific subgroup of alcoholics.
Johnson BA, Roache JD, Javors MA, *et al.* (2000). *JAMA.* 284(8): 963-971.

Use of Deception by Internal Medicine Residents

Although the use of deception by physicians in encounters with their patients has been intensely scrutinized, little is known about the practices of lying by physicians in their interactions with their colleagues. In a survey of 222 internal medicine residents at four teaching hospitals in the United States, respondents were presented with five clinical vignettes and were asked to indicate their willingness to deceive their colleagues in each scenario. 36% of respondents indicated that they were likely to use deception to avoid exchanging call with a fellow resident, while 6% would protect a colleague by substituting their own urine in another resident's drug test. With regard to patient care, 15% indicated that they would misrepresent a diagnosis in a medical record to protect a patient's privacy, 14% would fabricate a patient's laboratory data if asked to recall it by an attending physician during rounds, and 5% would lie to an attending physician about checking a patient's stool for blood to cover up their own medical mistake. The authors of the study suggest that while lying about clinical issues is not common, it is troubling when it occurs. They recommend that professionalism and collegiality should be addressed as part of the medical education curriculum and that educators should consider the possibility that a resident is not telling the truth as part of the differential diagnosis in a patient work-up.
Green MJ, Faber NJ, Ubel PA, *et al.* (2000). *Arch Intern Med.* 160:2317-2323.

Free Estradiol May Protect Against Dementia in Women

Previous studies have yielded conflicting results on the question of whether estrogen replacement therapy can improve cognitive function or prevent Alzheimer's disease in post-menopausal women. Estrogen receptors are expressed throughout the brain, particularly in regions involved in memory and learning, such as the hippocampus and amygdala. Unlike previous authors who investigated the relationship between total serum estrogen and cognitive performance, Yaffe and colleagues hypothesized that concentrations of non-protein-bound (free) and loosely bound (bioavailable) estradiol might be associated with cognitive function in older women. 425 post-menopausal women aged 65 or older underwent cognitive assessment with a modified mini mental status examination (mMMSE) and measurement of free and bioavailable serum estradiol by radio-immune assay at baseline and six years later. Cognitive impairment (a decrease of 3 points or more in mMMSE score) occurred in five of 94 women in the high tertile for free estradiol and in 17 of 106 women in the low tertile. This association persisted after adjustment for age, education, body mass index, current estrogen use, history of surgical menopause and baseline mMMSE score. The authors speculate that free estradiol might be more important in protecting against cognitive decline because of its increased bioactivity and increased ability to cross the blood-brain barrier, as compared with total estradiol, which is largely bound to sex-hormone binding-globulin in the bloodstream. The authors note that all of the women in the study had relatively low levels of free estradiol and suggest that a low dose of estrogen replacement therapy might be sufficient to prevent cognitive decline, without significantly increasing the risk of negative outcomes, such as breast cancer or thrombosis.
Yaffe K, Lui L-Y, Grady D, Cauley J, Kramer J and Cummings SR. (2000). *Lancet.* 356: 708-712.

Insulin Independence Following Islet Transplantation in Seven Type I Diabetics

Previous studies of islet transplantation in type I diabetics with poor glycemic control have failed to consistently yield sustained freedom from the need for injected insulin. Many of the immunosuppressive agents used in previous transplantation regimens, such as diabetogenic glucocorticoids, either damage the insulin-producing beta cells of the pancreas or induce resistance to insulin in peripheral tissues. To address this problem, Shapiro and colleagues designed a regimen to transplant pancreatic islets in conjunction with glucocorticoid-free immunosuppressive therapy. Seven type I diabetics with a history of severe hypoglycemia and metabolic instability received islet transplants. All seven patients quickly achieved insulin independence following transplantation of sufficient numbers of islets and remained free of the need for exogenous insulin as of their most recent follow-up (mean: 11.9 months). All patients demonstrated markedly improved glycemic control, indicated by a significant mean decrease in the amplitude of glycemic excursions, a return to the normal range of glycosylated hemoglobin values and absence of episodes of hypoglycemic coma following transplantation. Three and six months after transplantation all patients had detectable serum C-peptide concentrations, indicating that the transplanted islets were producing endogenous insulin. There was no evidence of serious transplant-related complications. In summary, these findings indicate that islet transplantation in conjunction with glucocorticoid-free immunosuppression can result in insulin independence and good metabolic glycemic control in patients with type I diabetes.
Shapiro AMJ, Lakey JRT, Ryan EA *et al.* (2000). *NEJM.* 343(4):230-238.

New Protein Inhibits Colon Cancer

Jamie I. Spiegelman, B.Sc., (OT4)

Colon cancer is the second-leading cause of cancer deaths in North America and it has been estimated that 50% of people develop colon tumours by the age of 70. Research by Sasaki and colleagues showed that genetic inactivation of the protein p110α produced an increased rate of colorectal cancers in mice. p110α is a catalytic subunit of the phosphoinositide-3-OH kinase α(PI(3)Kα) isoform that is activated by interaction with G-protein coupled receptors. PI(3)Ks are lipid kinases involved in the regulation of basic cellular responses, including cell proliferation, differentiation and protection from apoptosis. The researchers also found that p110α was not expressed in primary colorectal adenocarcinomas in human patients. When p110α was introduced into human colon cells lacking it, tumour formation was inhibited. Moreover, overexpression of p110α in human colon cancer cells with inactivating mutations in tumour suppressor genes (APC and p53) or in colon cancer cells with activating mutations in oncogenes (beta-catenin and K-ras) suppressed tumorigenesis. This data correlates well with their findings that mouse cells lacking p110α showed an increased expression of a cell death inhibitor (Bcl-2) and some important cell-cycle regulatory molecules (Cyclin D1, Cdk2 and Cdk4). Thus, p110α is a novel tumor suppressor gene that is able to negatively regulate multiple steps of colorectal tumor progression. It is thought that the prevalence of colon cancer is influenced by environmental factors such as diet. As a result of its involvement with G-protein coupled receptors expressed on the surface of colonic epithelial cells, the authors speculate that p110α may act as a messenger between environmental influences and cellular functions. Further study on the protein and its functional pathway to inhibit colorectal cancers may lead to improved treatment.
Sasaki T, Irie-Sasaki J, Horie Y *et al.* (2000). *Nature.* 406: 897-902.

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The 2000 Gairdner Awards

Rohit Bose, B.Sc. (M.D./Ph.D2)

The Gairdner Foundation International Awards are arguably the most prestigious Canadian awards for medical research. They are awarded to individuals who have made outstanding discoveries or contributions to medical science. Each year, three to six winners are chosen. The nomination process is international in scope and a panel of scientists from Canada, the United States and Great Britain chooses the award recipients. At an award ceremony in Toronto, they receive $30,000 and a sculpture, "Le Coeur". First awarded in 1959, they are the brainchild of James A. Gairdner, a Toronto businessman who suffered from severe arthritis and developed a deep respect for medical research. However, despite their own prestige, the Gairdner Awards have become most famous for their predictive value: 52 of the award's 256 recipients have gone on to win a Nobel prize.

Gairdner Award Winners, 2000

Roger D. Kornber, Ph.D. and Robert G. Roeder, Ph.D.

Dr. Kornberg and Dr. Roeder are recognized for their studies on the transcription machinery and elucidation of the basic mechanisms of transcription in eukaryotic cells.

Dr. Roger Kornberg's first major contribution to molecular biology came as a postdoctoral fellow at Cambridge, when he proposed the nucleosome model of chromatin structure. In order to understand the functional significance of nucleosomes, his attention turned to transcription. Dr. Kornberg receives the Gairdner Award for his essential contributions in describing much of the transcription apparatus, as well as the mechanisms and regulation of transcription. Earlier this year, the crystallographic structure of RNA polymerase II was elucidated in his laboratory. Currently, Dr. Kornberg is a professor in Structural Biology at Stanford University School of Medicine.

Like his co-recipient of this award, **Dr. Robert Roeder** also made his mark early. As a graduate student at the University of Washington in Seattle, he discovered all three of the eukaryotic RNA polymerases. He went on to study the polymerases' mechanism of action and subcellular localization. Dr. Roeder also developed test-tube assays for the initiation of transcription, which greatly furthered the characterization of the transcriptional apparatus. He is further credited with the discovery of the first eukaryotic gene-specific activator. Dr. Roeder is the Arnold and Mabel Beckman Professor of Biochemistry and Molecular Biology at the Rockefeller University of New York.

Alain Townsend, M.D., Ph.D. and Emil Unanue, M.D.

Dr. Alain Townsend and Dr. Emil Unanue are recognized for elucidating the mechanisms of antigen processing, the physiological role of histocompatibility molecules and T lymphocyte antigen recognition.

Professor Alain Townsend greatly furthered the field of immunology by discovering that cytotoxic T cells recognize peptides associated with major histocompatibility (MHC) molecules. He went on to delineate the role of antigenic peptides in the assembly and expression of MHC Class I molecules. This major contribution led to the discovery of peptide transporters in the endoplasmic reticulum. Dr. Townsend is a Professor of Molecular Immunology at the Institute of Molecular Medicine and an honorary consultant in General Internal Medicine at John Radcliffe Hospital, Oxford University.

In the late 1960s, **Professor Emil Unanue** put forward the revolutionary suggestion that proteins became more immunogenic after their phagocytosis and subsequent catabolism by macrophages. He went on to discover that protein antigens are internalized and broken down into short peptides by antigen-presenting cells. Professor Unanue elucidated the function of MHC Class II molecules: they bind to these peptides and activate T cells. He is currently the Pathologist-in-Chief at Barnes-Jewish Hospital, and the Professor and Head of Pathology and Immunology at Washington University in St. Louis.

Jack Hirsh, C.M., M.D., F.R.C.P.C, F.R.A.C.P., F.R.S.C., D.Sc.

Dr. Jack Hirsh is recognized for his pioneering contributions to our understanding of the diagnosis, prevention and treatment of thromboembolic disorders.

Originally from Australia, **Dr. Jack Hirsh** has made a number of significant contributions in the area of thromboembolic disorders. He developed diagnostic techniques that have improved the diagnosis of these disorders. His studies of the anticoagulants heparin and warfarin set the international standards for their dosing. Dr. Hirsh was also involved in the development of low-molecular-weight heparin. His approach to clinical research has formed much of the basis for modern "evidence-based medicine," and he is considered to be one of the founding fathers of McMaster medical school. Following his residency, Dr. Hirsh trained at the University of Toronto among other places before joining the faculty at McMaster University. Currently, he is the Director of the Hamilton Civic Hospital Research Centre.

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Prolific Scientist Profiles

An Interview with Dr. Jack Hirsh, 2000 Gairdner Award Winner

Rohit Bose, B.Sc. (M.D./Ph.D.2)

Dr. Jack Hirsh, the Director of the Hamilton Civic Hospital Research Centre, was recognized with a 2000 Gairdner Award for his landmark work in thromboembolic disorders. *News and Views* spoke with Dr. Hirsh about his beginnings in research and his views on the relationship between academia and industry.

N&V: Dr. Hirsh, what led you to medieal researeh?

JH: During medieal sehool and resideney, I realized that we didn't have good evidence to support most of the things we were doing, and I thought that I'd really like to explore that. Then I did four years of researeh after finishing my internal medieine and haematology in three different places: USA, England and Toronto. I came baek to Australia in 1967 as an associate professor in the department of Medicine. I was responsible for running a ward of about 30 patients in haematology. It was a real culture shock to me, beeause until then, I had worked in laboratories where you ask speeifie questions, and applied the scientifie method to answer them. [On the ward,] when I asked about the things we did, I was simply told that this is what we do. I began reading the literature, and often found what we did was not supported by evidenee, and in faet, there was data to suggest an alternative approaeh. It was very difficult to change people's praetice, beeause many of the physieians didn't read. So, I thought evidence-based elinieal praetiee was far behind evidence-based basic seienee.

Then, Dr. J. Fraser Mustard (5T3) asked me to visit him at MeMaster. There, I met a number of exeiting people, and it beeame clear, with that environment, we could start developing rules for an evidenee-based approaeh. Until then, elinieal researeh was defined as an M.D. working in a lab on basie aspects of scienee, and then emerging from the lab to see patients. And what the physician-seientist did in the lab, and what he/she did in the clinic were totally unrelated. That had to be redefined, I felt and I believe we did redefine it. That's why I got the Gairdner award. So basieally what we then began to develop was a group of physieians who understood elinieal epidemiology but who were also experts in their particular elinieal field. In order to do elinieal researeh, you must have the expertise to know which questions are worth asking and, of eourse, you have to have the methodologieal skills to make sure they're asked the right way, and that they're analyzed eorreetly. As you know, I'm in the thrombosis field. It's impossible to do that without a very strong lab baeking. I think that in the definition beneh-to-bedside, you've got to have a strong beneh, not only do you have to be strong at the bedside, but you also have to understand how to ask the right questions.

N&V: How did you get into thrombosis?

JH: One of my mentors in Australia told me there was a very important area whieh transeends haematology and eardiology, and no one seems to be doing much in that area. His name was Dr. Carl deGruchy.

In addition to his storied academic career, Dr. Hirsh is also vice-president of Vascular Therapeutics Inc., a pharmaceutical company which was created to commercialize therapeutics developed at the Hamilton Civic Hospital Research Centre. He shared his views on the relationship between academia and industry:

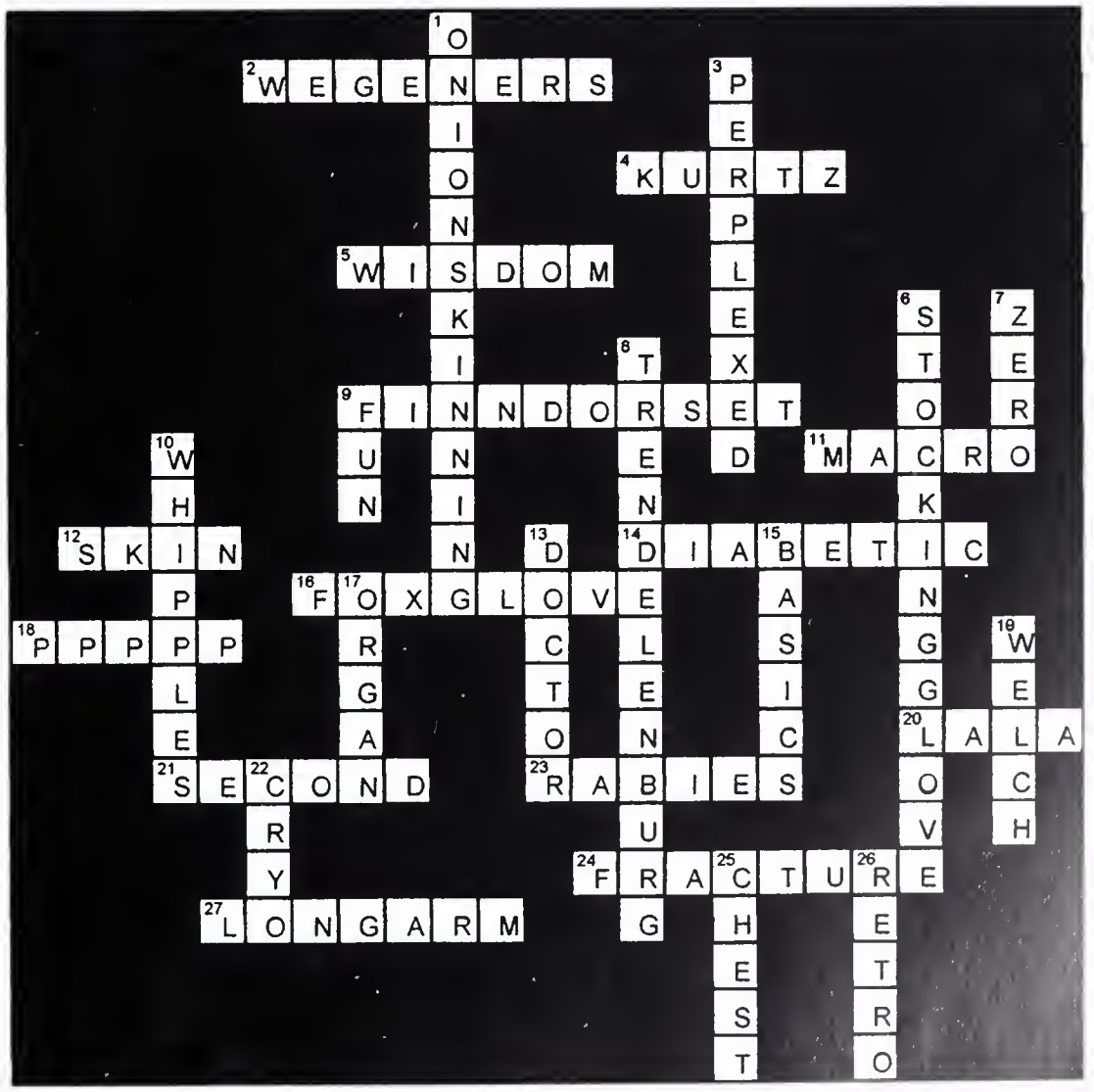
JH: There are potentially eonflieting interests, so I wouldn't say the whole thing's simple. But I felt the approach of old was disadvantaging the academies. Until about ten years ago, aeademie institutions would provide the patients and expertise to help industry develop products that would make [industry] more money. In fact, we were involved in the initial development of low-moleeular-weight heparin and we didn't get anything out of it. I don't regret it; that was a fact. When I moved to [McMaster], we began to develop some neat ideas. I thought, perhaps we should take them a little further, rather than just rapidly publish. There are two problems with rapidly publishing: one is these days, it's likely that the idea will never be applied, because in order to have an idea applied, to develop into clinical studies, it has to

have value. In other words, there has to be capital, it has to be protected. So, if someone developed a molecule, hypothetically, that worked in diabetes and published it, that molecule will probably never be used to treat diabetics, because millions of dollars will be required to conduct the clinical studies. And who's going to invest in millions of dollars, if they can't make any money at the end. At that stage, the venture capital industry hadn't started in Canada. I had a contact in California; and that's when we developed a company called Vascular Therapeutics. I was the chief scientist and we organized a mutual beneficial arrangement with the hospital and university; they had stock and so forth. So, if these ideas make lots of money, the hospital and university will benefit much more, as well as the scientist. The advantage of doing this is that research is accelerated tremendously for two reasons: there is more money infused into research and there is an accountability to hit timelines that does not exist in ordinary academic research. The downside is that only research which could be commercialized would be supported in the future and that would be wrong. So I think it's very important to strike a balance. But I think it's important that when scientists develop ideas, they and the institutions that develop them should benefit financially. This is being done in Toronto, for example, with Tak Mak. Particularly now, as research is much more expensive. And although the government is becoming a little more generous, you couldn't do competitive research. You can in the States, because they get more money. But you couldn't in Canada, or at least it's very difficult.

N&V: Could you describe the research training experience you had at the University of Toronto?

JH: I worked at a research institute established by Dr. Fraser Mustard. It was affiliated with U of T, but it was free standing. It was actually a very well equipped laboratory which has since been pulled down, and replaced with the planetarium. All the places where I did basic science research were excellent (London Postgraduate Hospital, Washington University at St. Louis and Toronto), but I'd say my time with Dr. Mustard at the University of Toronto was the most productive. And that influenced me in coming back to Canada. It's a big move to uproot your family and move to another country. I enjoyed my time in Canada tremendously. I liked the people and the culture so it was a pretty easy decision to make.

Crossword Answers – We hope you enjoyed it!



Back to Basics IV

Fracture Management

Murray Beuerlein, M.Sc (OT3), Chris Hall, B.Sc (OT3), and Emil H. Schemitsch, M.D., F.R.C.S.(C)

Initiated last year as a series of articles intended to provide a review of various diagnostic tests, *Back to Basics* will widen its scope this year to include discussions about fundamental aspects of clinical management and treatment in a variety of disciplines which are of interest to both physicians and medical students. This year's first installment provides a brief synopsis of the important clinical points to consider when managing a fractured bone.

Introduction

A solid working knowledge of the issues surrounding the management of fractures and their complications would prove to be a useful tool for any clinician. Though the majority of these injuries are treated by orthopedic surgeons and emergency physicians, other practitioners should be aware of the basic elements of this division of medicine in order to better serve their patients. In particular, the clinical approach to fractures and their associated complications is a fundamental skill which all physicians should possess. With this in mind, the following article will aim to provide a brief but comprehensive review of fracture management, with an emphasis on the clinical problems encountered on a regular basis by physicians and students alike.

Classification of Fractures

A fracture is a complete or incomplete disruption in the continuity of a bone.[1] There are several important characteristics of fractures that need to be identified to assist in the classification and management of the fracture. For example, fractures can be classified by the direction of the fracture line with respect to the long axis of the bone – (a) transverse, (b) oblique, or (c) spiral (Figure 1). They are also categorized by the anatomical location of the fracture - (a) proximal, (b) middle, or (c) distal one-third (Figure 2). Additionally, the degree of fragmentation – (a) segmental (dividing bone into several segments) or (b) comminuted (a fracture that has more than two fragments) – is an important consideration (Figure 3). It is also important to identify the type and degree of displacement. Fracture displacement occurs when one of the fragments shifts relative to the other. When characterizing the displacement, the position of the distal fragment is given with respect to the proximal fragment. The surfaces that remain in contact are said to be opposed, and the level of apposition is described as the percent of bony surface that remains in contact. Displacement of a fracture can occur in several ways. For example, the fracture fragments can be angulated in the anterior-posterior or sagittal planes. Furthermore, translation of the fracture fragments can occur and lead to instability and loss of coronal apposition. It is also important to note the rotational orientation of the fracture fragments. Malreduction of the rotational component can be difficult to judge on radiographs and can lead to permanent deformity if left untreated. It is also important to determine if the fracture involves any adjacent joint; if so, it is said to be an intra-articular fracture. The treatment of intra-articular fractures requires anatomical reduction of the fracture fragments to restore the articular surface. Otherwise, joint incongruity will lead to early onset of osteoarthritis in the affected joint. Other common descriptions of fractures include compression or crush, impacted, and greenstick fractures. Greenstick fractures are incomplete fractures that break only one cortex completely.[2] They are common in children due to the increased flexibility and thicker periosteum in the bones of children.

Fractures are also categorized as open or closed. Open fractures are injuries in which there is direct communication between the fracture fragments and the external environment. Open fractures are serious injuries with increased risk of vascular and nerve damage because they tend to result from high energy injuries. However, the most dangerous risk associated with open fractures is infection. The communication with the external environment provides a route for bacteria to gain access to the wound. This is not an issue in cases of closed injuries.

The pattern of fracture is important in that it may give clues about the mechanism of injury, the method of reduction, and provide insight into the stability of the fracture. The classification of fractures is summarized in Table 1. Transverse fractures commonly arise from angulation force, whereas spiral fractures result from a twisting force applied to the bone (Table 2). The pattern may also give an indication of the stability of the fracture. For example, transverse fractures tend to be stable and remain reduced. However, with oblique, spiral, or highly comminuted fractures, maintaining reduction is more difficult. This generalization is clouded by the fact that transverse fractures are often associated with high energy fractures in which the concomitant soft tissue damage is extensive, which may reduce the stability at the fracture site.

Most fractures are the result of a single, sudden injury. However, repeated loading can also lead to a fracture - known as a stress or fatigue fracture. These fractures are rarely displaced and are often not evident on radiographs for two to four weeks. Alternatively, some fractures result atraumatically or from trivial trauma in bone

that has been weakened by disease. These are referred to as pathological fractures, and can be seen in patients with diseases of the bone such as osteogenesis imperfecta, osteoporosis, Paget's disease, osteomyelitis, and benign or malignant tumours.[1]

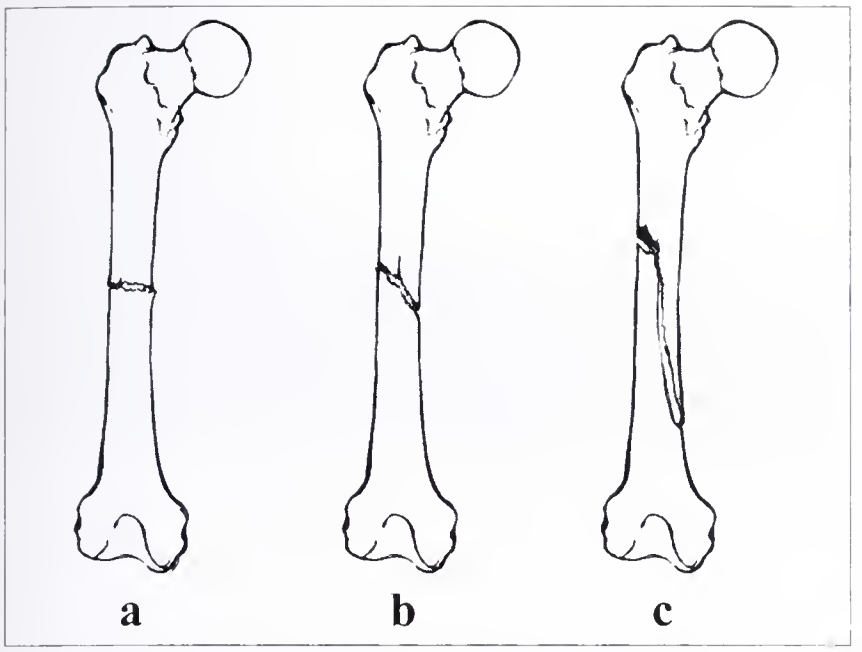


Figure 1. *Typical fracture pattern of long bones. The fracture pattern is classified by the direction of the fracture line with respect to the long axis of the bone:. (a) Transverse, (b) Oblique, and (c) Spiral.*

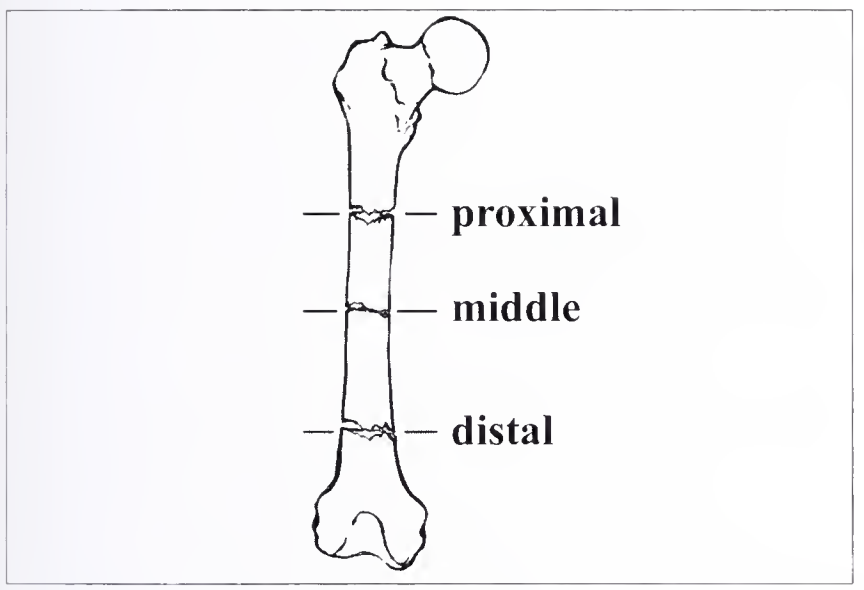


Figure 2. *Anatomical location of long bone fractures. The fracture is described as occurring in the proximal, middle or distal thirds of the bone.*

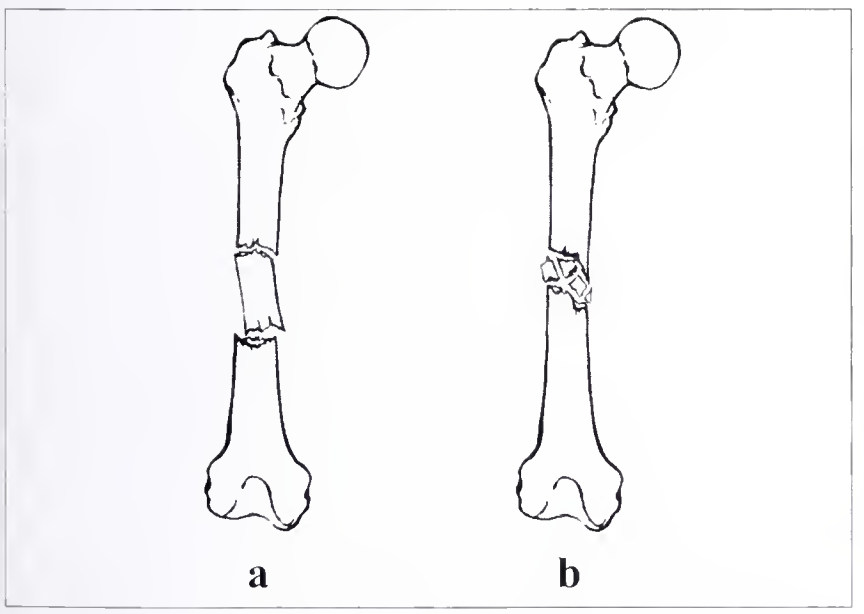


Figure 3. *The degree of fracture fragmentation. (a) Segmental fractures divide the bone into several segments, whereas (b) Comminuted fractures have multiple fragments at a single fracture site.*

Table 1
Classification of Fractures

Characteristic	Description
Soft Tissue Involvement	Open, Closed
Direction of Fracture Line	Transverse, Oblique, Spiral
Anatomical Location	Proximal, Middle, or Distal Third
Degree of Fragmentation	Segmental, Comminuted
Articular Involvement	Intra-Articular, Extra-Articular
Stability	Stable, Unstable
Other Descriptive Terms	Compression, Impacted, Greenstick

Table 2
Mechanism of Injury in Common Fracture Types

Fracture Type	Force Applied
Avulsion	Traction
Transverse	Angulation
Spiral	Rotational
Oblique	Axial Loading and Angulation

Fracture Healing

The healing of bone is unique in that it leads to the formation of healthy bone that is equivalent to the rest of the bone, whereas most other tissues heal by the formation of scar tissue that is functionally weaker than the original tissue. Fracture healing can occur by two different mechanisms depending on the characteristics of the fracture and the method of fixation. Non-displaced fractures and fractures treated with anatomical reduction and rigid internal fixation with compression across the fracture site (*i.e.* plating) heal by the process of primary bone healing. When there is direct contact between the cortical bone ends, osteoblasts traverse the fracture site and lay down lamellar bone without forming a woven or immature bone intermediate.[3]

In fractures that are displaced and those treated by casting, external fixation, or internal fixation devices (such as intramedullary nails) there is no compression across the fracture site and motion can occur at the fracture site. As a result of the motion, fracture callus forms in an attempt to stabilize the bone fragments. The healing of a fracture with callus is a process known as secondary fracture healing.

Repair of tubular bone via secondary fracture healing occurs in five stages[1]: (1) stage of hematoma, (2) stage of periosteal and endosteal proliferation, (3) stage of callus, (4) stage of consolidation, and (5) stage of remodelling.

The extent of callus formation is determined by factors such as (1) the amount of motion at the fracture site during healing, (2) the degree of displacement of the fragments, (3) the amount of periosteal stripping, and (4) the size of the fracture hematoma. Increasing the extent of these four factors will tend to increase the

formation, whereas decreasing these factors will ... the size of the callus.

... rigid fixation of fractures allows for primary bone healing without the cartilaginous callus intermediate, it does not accelerate fracture healing or produce stronger bone.[2] Rigid internal fixation of fractures and the resulting primary bone healing is beneficial in that it allows patients early limb motion and minimizes the delay in returning to activities. This is advantageous in that it minimizes stiffness and muscle atrophy, while retaining the range of motion.[2]

Clinical Approach to Fractures

Step 1: The History

As one might expect, the history presented by most patients with a suspected fracture will contain a readily apparent mechanism of injury, such as blunt force trauma, a fall, or some other form of high-energy stress applied to the injured area. The presenting symptoms are also quite predictable, since they will often include pain, swelling, loss of function, and occasionally a noticeable deformity.[4] In some cases, crepitus and movement between the fragments may also be noted.[1] The prudent clinician would do well, however, to note that not all fractures will present in such a typical fashion; a well-conducted history will thus attempt to elucidate factors which may predispose the patient to pathological fractures.

Step 2: The Physical Examination

As with the history, the physical examination of a patient with a suspected fracture may at first glance appear to be very straightforward. The site of the fracture will usually be obvious, since local tenderness, edema, and ecchymosis (visible bruising) are often present in the area of injury. As mentioned previously, there may also be a bony deformity evident upon examination, and movement between fragments, with or without crepitus, may also be noted.[1] It is crucial to note, however, that the physical examination should not cease once the simple task of delineating the area(s) of bony injury has been completed. The following clinical investigations must also be performed to prevent the occurrence of various undesirable sequelae:

1. Evaluate the Airway, Breathing and Circulation ("ABCs") in traumatic cases and begin prompt supportive measures when necessary.
2. Assess the patient for signs of hemodynamic instability (suggestive of a major arterial or visceral injury resulting in hemorrhage) and secure surgical care for cases that warrant it.
3. Explore any open wounds to ensure that they do not communicate directly with the fracture fragments; if this is indeed the case, the wounds must be treated surgically to prevent infection.
4. Assess the warmth, color, peripheral pulses and 'capillary return' distal to fractures of the limbs to prevent ischemic complications.
5. Assess the patient for the cardinal signs of compartment syndrome (see below).
6. Prevent neurological complications by assessing peripheral nerve function distal to the injury.
7. Observe the patient over several days in cases with a high risk of fat emboli (see below).

Step 3: Laboratory and Radiologic Investigations

Radiological examination is one of the cornerstones of fracture assessment. When requesting a series of X-rays to evaluate a potential fracture, two important points must always be kept in mind:

1. At least two views of the injury, taken at right angles to each other, should be obtained.
2. Joints which may have absorbed some of the force causing a traumatic injury should be examined for the possibility of intra-articular fractures. A general rule is to obtain views of the joints immediately above and below the area of acute injury.[5]

In addition to demonstrating traumatic fractures, X-rays may reveal disease processes which can predispose a bone to pathological fractures such as metastatic disease or osteoporosis.

Step 4: Obtaining Reduction of the Fracture

The treatment of uncomplicated closed fractures (not associated with neurovascular or visceral injury) follows three fundamental principles: (1) obtaining reduction, (2) maintaining reduction, and (3) rehabilitation.

Reduction, the act of restoring the fracture fragments to their normal anatomical relation, can be performed by three general techniques. The first is closed reduction, which is the standard initial method of reducing most common fractures. Closed reduction is performed by grasping the fracture fragments and adjusting them to their normal anatomical position. Secondly, reduction can be performed using mechanical traction, which is often necessary when large muscles are exerting strong forces on the fracture fragments. The third option is open reduction in which the fracture is reduced by means of an operative procedure. Open reduction of a fracture is indicated in the following situations: (1) non-union, (2) open fracture, (3) neurovascular compromise, (4) intra-articular fractures, (5) special situations such as fractures of the femoral neck or talar neck, and (6) polytrauma. If patients require an open reduction, it is generally accepted that one should perform an internal fixation of the fracture during the operative procedure.

Step 5: Maintaining Reduction of the Fracture (Immobilization)

Immobilization of the fracture is carried out for three purposes.[2] First, immobilization helps to prevent displacement or angulation of the fragments. For example, fractures of long bones usually require immobilization to maintain the reduction. Secondly, immobilization reduces the motion of the fracture fragments which may otherwise lead to non-union. However, there are fractures that unite spontaneously and remain reduced without rigid immobilization. These include fractures to the ribs, clavicle, and many of the metacarpals, metatarsals and phalanges. In these situations, excessive immobilization may do more harm than good. For example, prolonged immobilization of the hand can lead to permanent stiffness of the joints and decreased function of the extremity and is, therefore, contraindicated in fractures of the hand. The third goal of immobilization is to relieve pain. As a result of pain relief the patient is more comfortable and can use the limb more effectively.

There are four principle methods of maintaining reduction of fracture fragments. These include (1) casting or other external splinting, (2) continuous traction, (3) external fixation, and (4) internal fixation.

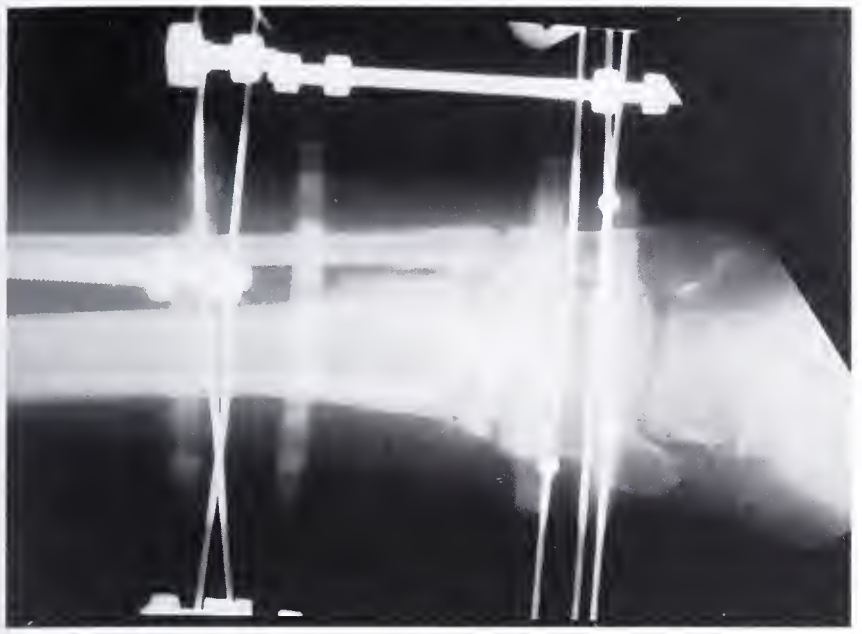


Figure 4. *External fixation of distal tibia nonunion. Pins are inserted into the fracture fragments and are held in place by rigid rods that are external to the skin.*

Table 3
Indications for Internal Fixation of Fractures

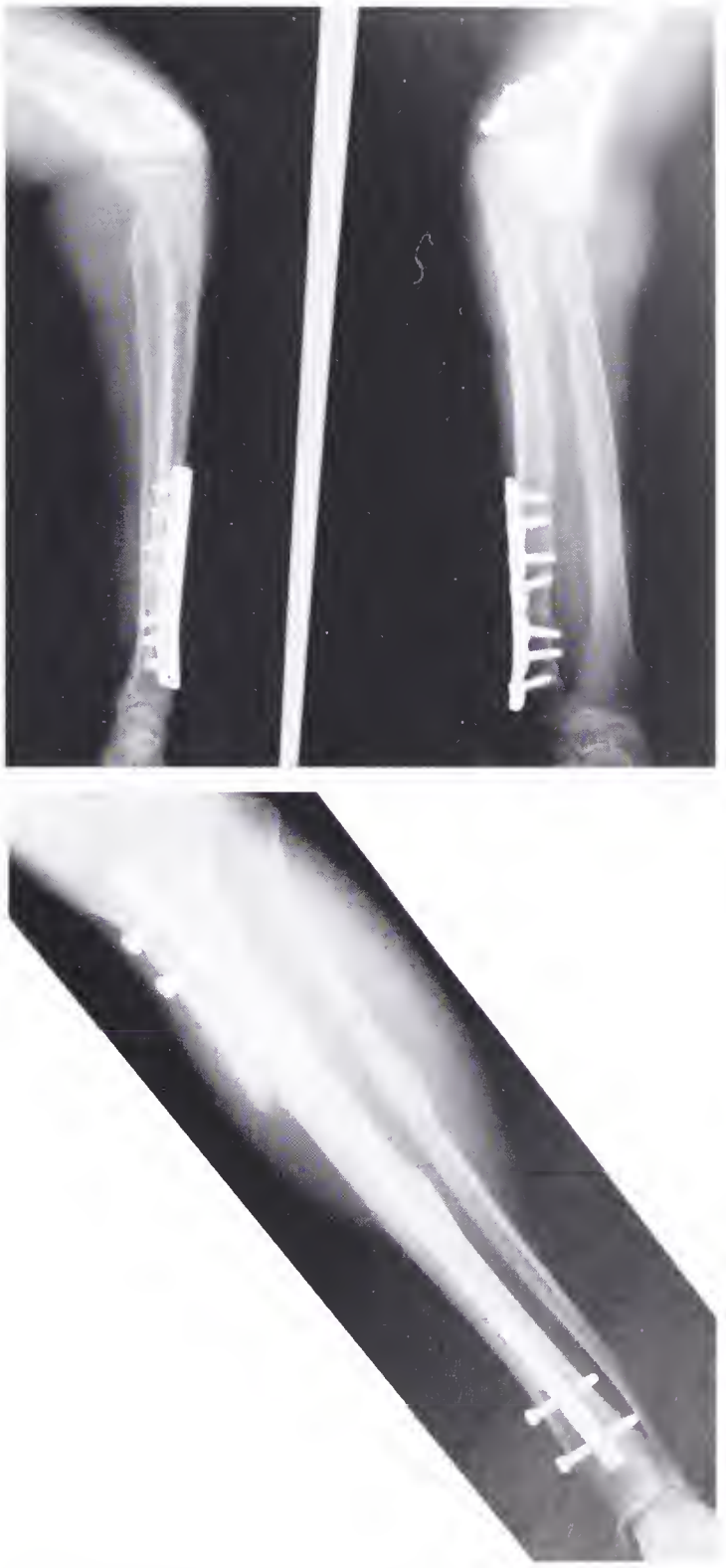
Pathologic Fractures
Open Fractures
Neurovascular Compromise
Failure to Obtain Reduction
Failure to Maintain Reduction
Poly-Trauma
Anatomical Reduction Necessary:
Intra-Articular Fractures
Sites at High Risk of AVN *e.g.* Head of Femur, Talus, Scaphoid
Special Circumstances:
Femoral Shaft, Forearm

The Plaster of Paris cast is the standard method for immobilizing most fractures.[1,2] One of the risks of casting fractures is the loss of circulation due to swelling of the local tissues. Swelling is maximal in the first forty-eight hours after a fracture. Severe pain within the cast and swelling of the extremity are two signs of impaired circulation, and require removal and resplinting of the fracture. Functional bracing is a form of casting of long bones that supports the extremity so that the function of adjacent joints is maintained and the use of the limb for normal activity can be preserved.

Continuous traction has been used historically as a means of fracture immobilization before external and internal fixation devices became commonplace. Today, however, the role of continuous traction has been reduced to the treatment of some pediatric fractures in which surgical correction is contraindicated.

External fixation is a system of rigid anchorage of bone fragments to an external device (such as a bar via pins) inserted into the fracture fragments (Figure 4). The primary application of external fixation is to open or infected fractures in which internal fixation is deemed undesirable. For specific fractures, external fixation is the treatment of choice. These include fractures of the pelvis or distal radius, fractures with soft tissue compromise, and fractures associated with severe edema.

Internal fixation devices can be categorized as extramedullary devices such as plates, screws, and wires, and intramedullary devices such as nails (Figure 5). If open reduction of the fracture was necessary, internal fixation is generally performed.[2] A list of indications for internal fixation of fractures is described in Table 3. The benefits of surgical fracture fixation are fourfold. First, it minimizes the time spent in hospital and away from employment and recreational activities. Secondly, it allows an early return to function, thereby minimizing the loss of function of adjacent joints. Thirdly, surgical fixation may lower the rate of complications. Fourthly, internal fixation allows anatomical reduction of displaced articular fractures.



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5b

Figure 5. *Internal fixation devices. (A) A plate and screws are used to correct fractures of the distal humerus and distal ulna. Plates provide compression across the fracture site leading to primary bone healing without callus. (B) Intramedullary (IM) nail fixation of a proximal tibial fracture. Proximal and distal interlocking screws allow for control of both length and rotation of the fixation. IM nails do not provide compression across the fracture site, and as a result, secondary bone healing with callus occurs.*

Step 6: Rehabilitation

Rehabilitation is essential in recovering from a fracture. The purposes of rehabilitation are to preserve function while the fracture is healing and restore normal function to the adjacent joints once the fracture has united. Rehabilitation can take the form of active use in which the patient employs the injured limb as much as possible within the limitations of the injury. In addition, to help maintain the strength of adjacent muscles, isometric contraction exercises are recommended. Since articular cartilage is nourished by the synovial fluid within a joint, movement of the joint facilitates the distribution of synovial fluid and preservation of healthy cartilage. Based on this knowledge, continuous-passive-movement machines have been promoted to move joints and help preserve the cartilage in patients with fracture injuries.

Complications of Fractures

The management of fractures may often be complicated by any of a number of secondary clinical conditions, many of which can have dire consequences for the patient. Rapid recognition of the clinical signs produced by these complications is essential to the achievement of a desirable outcome, and is thus a valuable skill for physicians and students alike.

Life-Threatening Complications

Patients exhibiting symptoms consistent with any of the following conditions require the immediate attention of a physician, as their survival will depend upon the expedient delivery of care.

Fat Embolus Syndrome (FES)

An important cause of Acute Respiratory Distress Syndrome (ARDS), FES is occasionally seen during fractures of the long bones, especially the tibia and femur. Fat emboli and various biochemical factors released from the marrow of these bones by large fractures can act as catalysts, initiating damaging processes in organs throughout the body. The diagnosis of FES can be made on the basis of criteria established by Gurd and Wilson[6] in 1974 (Table 4) with the presence of one major clinical sign, four minor clinical signs and fat macroglobulinemia.

Disseminated Intravascular Coagulation (DIC)

This syndrome will manifest itself as a backdrop to many clinical situations, including widespread trauma. Its pathogenesis has not been well-elucidated, but it is known to involve a systemic dysfunction of hemostasis triggered by the primary clinical disorder. This leads to an over-consumption of clotting factors, causing widespread bleeding and potentially resulting in multiple organ damage and/or failure.

Thromboembolism

This complication has been noted in patients who have suffered skeletal trauma or undergone elective orthopedic surgery. For poorly understood reasons, thromboemboli form in the bloodstream of these patients and travel to the lungs, where they may cause acute respiratory failure.

Shock

Patients suffering from certain fractures are at grave risk of developing hypovolemic symptoms resulting from massive internal hemorrhage. For example, hip fractures disrupting the pelvic ring will often require a blood transfusion to ward off hypovolemic shock. In fractures of the femoral shaft, large amounts of blood loss may be concealed within the surrounding swollen tissue. The clinician should be ever-vigilant of the signs of tissue hypoperfusion in patients suffering from traumatic injury, and take measures to ensure the maintenance of blood volume.

Tetanus

Tetanus is caused by a toxin made by an infectious organism *(C. tetani)* which infiltrates even the shallowest of abrasions. It is characterized by spastic paralysis which may cause death through its effects on the muscles of the heart and respiratory system. Thus, fractures caused by a blow from a potentially colonized object should be assessed for breach of the overlying skin; prophylaxis with intramuscular tetanus toxoid may be necessary.

Limb-Threatening Complications

The following complications, if left untreated, may result in a clinical course which can lead to complete loss of function in the affected limb or even necessitate its amputation.

Compartment Syndrome

A widely-feared complication of fractures, this condition may lead to severe ischemic contractures of the muscles of the affected limb. The causative agent is a dramatic rise in the tissue pressure within a fascial compartment, leading to a drop in the amount of blood reaching the muscles within it. Sources of increased pressure include soft tissue swelling secondary to the fracture and tightly-applied dressings or plaster casts. In those cases where a major artery passes through the compartment in question, blood supply to distal structures may be compromised to the point where gangrene occurs and surgical removal of part of the limb is necessary. The cardinal signs of compartment syndrome are traditionally described as pain, pallor, paraesthesias, paralysis and distal pulselessness ("the 5 P's"),[5] but severe pain is the only reliable early indicator. An objective assessment can be achieved using an intra-

Table 4
Diagnostic Criteria for Fat Embolus Syndrome

Major Features	Minor Features	Laboratory Features
Respiratory insufficiency	Pyrexia	Anemia
Changes in neurological status (progressing from agitation to coma)	Tachycardia	Thrombocytopenia
	Retinal changes	High Erythrocyte Sedimentation Rate (ESR)
Petechial rash	Jaundice	Fat macroglobulinemia
	Renal changes	

muscular manometer to gauge the intracompartmental pressure. This condition requires prompt decompressive fasciotomy to save the muscles from irreversible damage.

Gas Gangrene

Another complication caused by bacteria, gas gangrene is a serious side effect of infiltration of a deep wound by *C. perfringens*. These bacteria produce toxins which can cause fulminant necrosis of the tissue surrounding the wound, and extensive spread of the infection may necessitate amputation of the limb. Proper surgical care of all open fractures, including debridement of any damaged tissues, is necessary to avoid this devastating illness. (Note: This complication will become life-threatening if left untreated, since the toxins may prove fatal if they gain access to the bloodstream.)

Vascular Damage

As previously mentioned, interruption of the blood supply to the distal parts of a limb may result in ischemic necrosis (gangrene). Gangrenous areas are very susceptible to infection, and must thus be amputated to prevent the development of septicemia. The discovery of a cold, pale, and pulseless limb on physical examination indicates a need for urgent reduction and splinting of the fracture, with consequent reevaluation of circulatory integrity. Persistence of poor circulation after primary care of the fracture may require surgical intervention to re-establish blood flow.

Figure 6. *Non-union of a proximal ulna fracture treated unsuccessfully with internal fixation. Non-union is characterized by rounding-off and sclerosis of the fracture fragments.*

Figure 7. *Osteomyelitis of the tibial shaft.*

Complications Having Local Effects

A number of fracture complications are known to have relatively localized effects which may result in a permanent deficit in the functional capacity of a limb or joint.

Union Disorders

This group of complications relates to the healing of fractures and includes delayed union, non-union (Figure 6) and angular deformities (mal-union). Their incidence varies according to the age of the patient, his/her general state of health, the bone fractured, the severity of the original injury, and the presence of infection in the bone (osteomyclitis) as seen in Figure 7.

Osteomyelitis

Direct innoculation of the bone with infectious organisms following an open fracture is the most common method of acquiring osteomyelitis. The resultant infection may become a chronic condition if not addressed properly, and it can play a role in the development of delayed union and non-union of fractures. Proper surgical debridement of all open fractures is an absolute necessity to prevent the occurrence of such infections.

Reflex Sympathetic Dystrophy (RSD)

This condition presents itself as a puzzling constellation of symptoms including pain, swelling, decreased range of motion and hyperaesthesia, long after the healing of relatively minor fractures in the limbs. These symptoms are often well out of proportion with the physical findings exhibited by the patient. Though the exact pathogenesis of RSD has not been well-defined, the presence of abnormal sympathetic reflexes seems to be a well-established feature.

Peripheral Nerve Damage

This complication may result from direct trauma to a nerve during the fracturing of a bone, or from a decrease in blood flow to a nerve secondary to the fracture (see above). The duration of the neurological deficits thus incurred will depend on the nature and severity of the damage sustained by the nerve. Bony injuries that commonly cause peripheral nerve injury are listed in Table 5.

Avascular Necrosis

Fracture fragments whose blood supply has been severed may ultimately undergo necrotic changes resulting in their collapse.[5] This

Table 5
Common Sites of Peripheral Nerve Injury Secondary to Bony Injury

Nerve Injured	Causative Injury
Ulnar nerve	Fracture of medial humeral epicondyle
Radial nerve	Fracture of shaft of humerus
Circumflex humeral nerve	Shoulder dislocation
Sciatic nerve	Hip dislocation with fracture of acetabulum
Common peroneal nerve	Fracture of fibular head; other knee injuries

Table 6
Common Sites of Avascular Necrosis

Necrosis	Causative Injury
Femoral head	Fracture through neck of the femur
Proximal scaphoid bone	Fracture through waist of the scaphoid bone
Lunate bone	Dislocation of the lunate bone
Body of the talus	Fracture through neck of the talus

Figure 8a. *Avascular necrosis (AVN) of the femoral head. (A) Early AVN is characterized by regions of sclerosis with patchy radiolucencies. Later stages would show collapse and deformation of the femoral head with osteoarthritic changes.*

Figure 8b. *Avascular necrosis (AVN) of the femoral head. (B) A normal femoral head is included for comparison. Note the uniformity of the normal femoral head compared to the patchy avascular head.*

complication is commonly seen after certain fractures (see Table 6), and in some cases may require reconstructive arthroplasty to restore the limb to a useful state. A radiographic example of avascular necrosis of the femoral head is shown in Figure 8.

Conclusion

The management of fractures and their complications is a task shared by a wide variety of physicians, from emergency practitioners to orthopedic surgeons to primary care providers. This article has aimed to provide a brief but comprehensive look at the major issues surrounding general orthopedic care, in the hopes that it may prove useful to both students and long-time MDs. For a more detailed treatment of these topics, the reader is directed to the references listed below.

References

1. Adams JC, Hamblen DL. (1999). *Outline of Fractures, Including Joint Injuries, 11th ed.* Churchill-Livingstone: New York.
2. Rockwood CA, Green DP. (1997). *Fractures, 4th ed.* Lippincott: Philadelphia.
3. Seligson D and Voos K. (1991). *The Primary Management of Musculoskeletal Trauma.* Lippincott-Raven Publishers: Philadelphia.
4. Eiff MP, Hatch RL, Calmbach WL. (1998). *Fracture management for primary care.* W.B. Saunders Company: Philadelphia.
5. Ahmed S, Cheung M. (1999). *MCCQE Review Notes and Lecture Series, 15th ed.* Webcom Limited: Toronto.
6. Gurd AR and Wilson RI. (1974). The fat embolism syndrome. *J Bone Joint Surg Br*, 56: 408.

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Law and Ethics in Medicine

The Ethics of Organ Donation: Examining Consent Policies and Donor Criteria

Denise Mackey and Maria Kjerulf, R.N., B.Sc.N.

Law and Ethics in Medicine
This section will explore current issues related to the legal and ethical dimensions of medical practice. This article focuses on the shortage of viable organ donations for transplantation and examines the ethical foundations of strategies aimed at increasing the number of organs available for transplant.

The disparity between the number of organs available for transplant and the number of patients on transplant waiting lists continues to grow. During 1999, 3529 patients were waiting for a solid organ transplant, while only 1745 of these patients actually received one.[1] During this time, 225 Canadians died while waiting for a transplant.[1] Waiting periods can range from two to six years, depending on disease acuity, medical suitability, and organ compatibility.[2,3] Longer waiting times lead to a greater disease progression at the time of transplant, which can compromise a patient's recovery or the survival of a graft. The impact that this "organ shortage" has on transplant waiting times is obvious, and requires an examination of present organ donation programs as well as possible alternatives that may serve to diminish the gap between available organs and waiting recipients.

Background Information

The current system of organ retrieval in Ontario recognizes only brain-dead patients as potential organ donors (with some exceptions, including single kidney and lung donors). Current policy dictates that consent must be obtained from the patient's next-of-kin before any organ or tissue may be removed for any purpose. Although individuals may record their wishes regarding donation on their driver's license or health card, such indications serve only as a guide to aid the family's decision. When seeking consent for donation in Ontario, health care professionals have few well-established guidelines to rely upon when trying to determine when and where the request should be made, and who should make it. Past studies have shown that donation rates are improved by allowing trained individuals to make the request away from the bedside during a specially-designated conversation separate from the one informing the family of their loved one's death (a process known as 'decoupling').[4,5] Studies such as these have recently begun to make an impact on the official policies surrounding the request process.[6]

Two systems which have been adopted by many Ontario hospitals to increase the number of organs available for transplant are 'routine referral' and 'required request'. The policy of routine referral requires that all incidences of imminent and/or actual brain death be reported to an organ procurement agency to determine if the organs are medically suitable for donation.[6,7] This practice has reduced the number of donors who are missed as a result of failing to identify their suitability for donation. The policy of 'required request', meanwhile, demands that the families of all potential donors be approached and offered the opportunity to donate their loved one's organs.[8-10] One of the greatest obstacles to improving organ donation rates is the commonly-held belief among health care professionals that consent cannot, or should not, be obtained from a grieving family. Such an assumption denies families the right to honour the last wishes of their loved ones. Required request policies effectively counteract these assumptions and allow for family members to make the final decision themselves.

Unfortunately, despite efforts to refine the routine referral and required request policies in Ontario, the gap between donors and recipients continues to grow.[11] Changes within the system aimed at narrowing this gap fall into two categories: those which address issues of consent, and those aimed at ratifying donor criteria. None of these changes, however, can be achieved without ethical implications. For each system of donation examined, one must consider the duty of non-maleficence for the health care provider, autonomy of the patient, promotion of the patient's well-being, and the need for a system that is non-discriminatory and just.

I. Consent Issues

The process of approaching families for consent to donate serves a number of purposes. Even if the patient's wishes are known, approaching the family recognizes the social relationships of the patient to the family and shows respect for the family. From a pragmatic point of view, it also serves to avoid adverse publicity that could result from honouring the patient's final wishes despite

their next-of-kin. Conversely, denying a patient the right to choose what will happen to them upon their death is contrary to individual autonomy. The expressed wishes of the individual serve as the basis for altruism and voluntarism in organ donation, yet family members can veto a patient's expressed wish at the time of death.

As a result of the known practice requiring familial consent, there may be little incentive for Canadians to sign a donor card and make their wishes publicly known. Consequently, many families are often unaware of their loved one's wishes at the time of death, making the decision more difficult at a particularly stressful time. A number of consent policies such as mandated choice, donor registries, and presumed consent exist as alternatives to the current system in Ontario, but the ethical implications of each warrant consideration. In order to gain the widespread public support they require to become successful, each proposed system must adequately balance the ethical principles of beneficence and justice. The ultimate goal of any changes made to the current system must be to provide the greatest possible benefit to society while maintaining the autonomy of the individual.

i. Mandated Choice

In a mandated choice system of consent, all competent adults must decide and record whether or not they wish to become an organ donor.[12-14] Mandated choice policies are often considered to be the most effective in terms of obtaining informed consent and preserving patient autonomy. Recording wishes in this manner relieves family members of the emotional stress associated with making this decision and grants it instead to the individual in a relaxed setting where the decision to donate can be given appropriate thought.[13] In this way, mandated choice strives to preserve individual altruism and voluntarism. A mandatory choice on the part of every citizen will also serve to increase public awareness of organ donation, since everyone would be required to consider the issue.

A number of concerns, however, are raised with respect to mandated choice laws. A large number of people are uncomfortable with contemplating their own mortality, and therefore any law mandating them to register a decision about organ donation could be construed as being coercive in nature. Also, if mandatory choice were to become practice, one must consider how familial involvement will be affected. If the family is still to be approached for donation, the recorded wishes of the patient would act as a guide to aid the family's decision, but there is no guarantee that these wishes would be honoured. Though studies have shown that families are rarely inclined to veto a recorded decision to donate, there remains a slight chance that the autonomy of the individual made possible by mandated choice could be undermined.[25] On the other hand, a practice in which the recorded wishes of the individual are final raises other implications. Policies that exclude family involvement entirely may feed suspicion and mistrust about organ retrieval, and could lead to an increase in the number of families that refuse donation.

ii. Donor Registries

Donor registries are considered less coercive than mandated choice, but strive for a similar effect. Individuals who wish to donate their organs after death are encouraged to register their wishes. In this form of registration, only "yes" decisions are recorded.[15] The registry is then consulted by the hospital upon the death of a patient to determine if a decision to donate organs was recorded. If so, that information is made available to health care professionals and facilitates the donation discussion with the family. Once again, however, if one registers a desire to donate organs after death, there is no guarantee that those wishes will be honoured. Since the family is given the authority to make the ultimate decision regarding donation regardless of a registered desire to donate, there is little incentive for individuals to register their wishes. As a result, many systems that operate under a registry policy have a low percentage of registration. British Columbia has been operating a registry since 1997, yet of the 3.3 million residents at or above the age of consent in this province, only 380,000 individuals are recorded in the registry.[16,17] Unless a registered yes decision was to be considered final, little is different from the current system. If yes decisions were to be considered final however, it does not solve the problem that exclusion of family members tends to be harmful to organ retrieval programs.

iii. Presumed Consent

In contrast to our present "opt-in" system, in which individuals must declare a desire to donate, presumed consent, or "opt-out", legislation requires individuals to declare a desire not to donate organs and/or tissues for transplantation.[18-20] A failure to indicate refusal, therefore, would be considered an implicit statement of consent. Such legislation presumes that the majority of society favours organ donation, thus justifying the routine retrieval of organs upon the death of a medically suitable donor. Presumed consent laws can be considered either "hard" or "soft".[13] Hard laws of presumed consent assert that individuals who have not recorded their desire to opt-out of organ donation are considered to have no objection, and organs are retrieved without family discussion. This is an extreme divergence from the current system in Canada, and is unlikely to be favoured by the public due to the associated risk of violating the autonomy of the individual.

Soft laws of presumed consent, on the other hand, operate much like our present system in that families are approached upon the death of a loved one. However, since retrieval of organs would be considered a routine procedure from which one may opt-out, families would be asked if they objected to the removal of organs rather than requesting explicit consent to do so. This approach is often considered more psychologically manageable, as the family would be spared the emotional stress of considering a procedure that is unfamiliar to them.[19] Families are also less likely to object to a routine procedure and more likely to be anticipating a discussion about retrieval, thus minimizing the "bad timing" effect that is often related to our current system of request. Presumed consent laws, however, must be coupled with extensive public education in order to obtain the public support that is crucial to the implementation of any such policies. Fears that presumed consent negates the voluntarism and altruism of donation could adversely affect public sentiment toward donation. The patient's right to choose must be emphasized when presenting presumed consent in order to avoid misinterpreting such policies as the "conscription of organs".

II. Donor Criteria

The transition from a "brain-dead only" criterion of organ donation to one which includes other patient populations is very delicate. One must consider the possible "slippery slopes" that arise from the inclusion of certain populations as well as the effects such criteria may have on the public's confidence in health care. Any medical policy seeking to alter the criteria for potential donors must be sensitive to society's fear that such measures may compromise the quality of health care, in order to avoid provoking mistrust and skepticism of organ donation programs. In considering expansion of the donor pool to include anencephalic donors, non-therapeutically ventilated patients, non-heart beating donors, and living donations, we must consider to what extent we can justify procurement of organs from these populations.

i. Anencephalic Donors

Anencephalic infants typically die from cardiopulmonary failure within hours or days of birth, and could represent a pool of potential organ donors for pediatric patients who are otherwise restricted by size.[21] As a result of their functioning brainstems, however, this population does not meet the criteria for brain death and is thus not currently considered to be an appropriate source of organs for donation. Establishing a diagnosis of anencephaly is complicated by a lack of consensus within the medical community as to the nature of the diagnostic criteria which must be met.[22] The absence of well-established clinical guidelines, combined with the variable life span of these infants, could give rise to ambiguity when trying to define with precision the criteria for inclusion of these patients into the potential donor pool. Furthermore, expansion of the donor pool to include this population could lead to the creation of a number of ethical "slippery slopes". For instance, how would the inclusion of anencephalic infants affect the donor status of other infants with conditions incompatible with life who also do not meet the criteria for brain death? In addition, inclusion criteria allowing for a limited amount of brain function might force many other patient populations, such as those in a persistent vegetative state, into a vulnerable situation. It is important that any discussion of anencephalic donation address these sensitive issues and propose appropriate safeguards for the slippery slopes that may result.

ii. Non-Therapeutic Ventilation

Non-therapeutic ventilation proposes that patients facing imminent death from a pathological intracranial event be transferred to an intensive care unit for ventilatory support until brain death occurs and organs can be retrieved.[9] In this scenario, patients who might become brain dead are therefore included as potential organ donors.[23] Although this practice could provide a substantial increase in the number of organs available for transplant, there are several consequences to be considered with respect to expanding the donor pool to include this population. Ventilation of these patients proposes no medical benefit. Even if consent from the family is obtained before ventilation is initiated, it raises concerns as to whether family members should be allowed to consent to a treatment that is not therapeutic for the individual patient. If non-therapeutic ventilation were to be initiated instead on the prior consent of the individual patient, further concerns may be raised. When attempting to establish advanced directives in terms of non-therapeutic ventilation, one must safeguard against misleading the patient about the ultimate purpose of this procedure. A clear distinction must be made between ventilation whose sole purpose is to allow for donation versus ventilatory support as a means of resuscitation. There is also a chance that ventilation of patients under such conditions may result in the patient lapsing into a persistent vegetative state.[13] Such a situation would raise further medical and ethical concerns for staff and family. Does the potential benefit of an increased number of organs available for transplant outweigh the risk to the patient? Furthermore, a higher influx of patients into intensive care units will also result in a greater demand for ICU beds, staff, and funding. Hospitals operating on fiscally balanced budgets would have to weigh the benefit to their transplant program against other hospital services.

iii. Non Heart-Beating Donors

Non heart-beating donors are those patients who are declared dead on the basis of cardiopulmonary rather than neurological criteria.[14,24] Death of these patients can be classified as either controlled or uncontrolled.[23] A controlled death occurs in the operating room, after the family has made a decision to terminate life support, and cardiac arrest is expected to follow. Therapy is withdrawn in the OR, and a waiting surgical team removes viable organs immediately after cardiopulmonary death has been declared. Uncontrolled deaths are characteristic of patients suffering from unexpected cardiac arrest which does not respond to CPR or other resuscitative measures. For these donors, steps must be taken to reduce the warm ischemic time of their organs in order to provide an opportunity to approach the next-of-kin for a discussion about organ donation. Procedures aimed at preserving organs in this way, including the placement of catheters for the perfusion and cooling of organs, must often be performed with little or no time to obtain consent from the family.[23] This raises concerns about the justifiability of preserving organs when the wishes of the patient regarding organ donation are not necessarily known. Another delicate issue to consider with respect to non heart-beating donors is the potential for damage to the public's trust in organ donation and the quality of end of life care. An opportunity given to a family to make donation possible can be easily construed as an attempt to take organs prematurely. Concerns about how death would occur in the operating room, as well as the fear that not all life saving measures will be taken in order to ensure donation, are public concerns that must be addressed before any such practice can be established in the health care system.

iv. Living Donation

Living donation is possible for kidneys as well as lobes of the liver, lung, and pancreas.[24] Living donation can fall into a number of categories, including genetically related donors, emotionally (but not genetically) related donors, and unrelated donors. The organs retrieved from a living donor are healthier and result in better graft and patient survival.[1] Living donation also permits transplantation to be performed electively, when the recipient is in optimal condition, and decreases the complications of organ preservation and ischemic injury.

Genetically related donors are often the most medically suitable for transplantation purposes. Donors not only benefit from the restored health of their loved one, but are also cited to have an increase in happiness and self-esteem from the altruistic act.[13]

Unfortunately, not all such donations are free of complication. [illegible] can decrease the autonomy of donation, and medically suitable family members often feel pressure to donate.[9] A [illegible] is also raised in regard to medically suitable children who cannot comprehend the associated risks of donation. Should proxy consent be allowed for these children to donate to a family member? Further implications arise for physicians in situations where a less medically fit family member wishes to donate. Should the donor be allowed to compromise their health status in order to donate an organ to a loved one? This dilemma is magnified in situations where parents are willing to accept significant risks to their health to provide an organ for their child.

Emotionally related donors are those with strong social ties to the patient, but who share no genetic relation. The donation of organs by these individuals is often considered to be a more autonomous act, as familial coercion is less likely to be an influential factor. However, ethical concerns remain about the motivation behind such an act. In such cases, it is difficult to monitor if there are any hidden incentives for donors, and these concerns have sparked debate over the extent to which a volunteer should be able to "direct" his or her organs to a specific individual. Not only would direction of organs be a violation of justice and contrary to allocation systems, but such a practice could lead to private campaigns for donors and could potentially escalate into a high-stakes market for suitable organs.

Conclusion

With the development of new transplantation methods and the heightening success of transplant medicine, we are facing a growing demand for organs that our present system cannot adequately meet. Alternative systems of consent and donor criteria should be scrutinized carefully in terms of their ethical and legal implications. The topics presented here were intended to illuminate the dilemmas faced by administrators and health care workers alike as they attempt to improve the organ retrieval system of this province. No solutions have been provided; it was the authors' intent to conduct an objective examination of the subject matter in the hopes that readers will continue to contemplate the ethical issues surrounding organ donation. Recent advancements in areas such as xenotransplantation and stem cell research promise to push these ethical debates to the forefront of our social conscience. Thus, a commitment to understanding the relevant problems in the present will serve to benefit both physicians and students in the future, as transplant medicine becomes a more prominent part of everyday medical practice.

References

1. Canadian Organ Replacement Register (1999). *1999 Report*, V.2.
2. Avolio A, Agnes S, Castagneto M. (2000). Ethical Implications in Donor-Recipient Allocation. *Transplant. Proc.* 32:81-82.
3. UNOS Rationale For Objectives of Equitable Organ Allocation. www.unos.org/Resources/bioethics_rationale_objectives.htm Feb. 22, 2000
4. Beasley C, Capossela L, Brigham L, Gunderson S, Weber P, Gortmaker S. (1997). The impact of a comprehensive, hospital focused intervention to increase organ donation. *J. Transpl. Coord.* 7(1):6-13.
5. Ehrle R, Shafer T, Nelson K. (1999). Referral, request, and consent for organ donation: best practice - a blueprint for success. *Critical Care Nurse.* 19(2): 21-33.
6. Premier's Advisory Board on Organ and Tissue Donation (2000). A Plan for Change and Action. Toronto. May 2000.
7. Shafer T, Kappel D, Heinrichs D. (1997). Strategies for success among OPO's: a study of three organ procurement organizations. *J. Transpl. Coord.* 7(1):22-31.
8. Robertson, V. National Conference on Organ and Tissue Donation for Transplantation. Toronto. June 2000.
9. Dunstan G. (1997). The ethics of organ donation. *British Medical Bulletin.* 53(4):921-939.
10. Caplan A. (1997). Requests, gifts, and obligations: the ethics of organ procurement. *Transpl. Proc.* 3(suppl 2):49-56.
11. Canadian Organ Replacement Register 1998 Report.
12. Spital A. (1996). Mandated choice for organ donation: time to give it a try? *Ann. Int. Med.* 125(1):66-69.
13. Spital A. (1999). Ethical and policy issues in altruistic living and cadaveric organ donation. *Clin. Transpl.* 11:77-87.
14. Siminoff L. (1999). Withdrawal of treatment and organ donation. *Critical Care Nursing Clinics of North America.* 9(1):85-94.
15. Allen N, Joyce D, Sutherland D. (1997)The Provincial Health Card and a Computer-Based Organ/Tissue Donor Registry in Canada. *Transpl. Proc.* 29(8):3231
16. Statistics Canada (2000). Population statistics. www.statcan.ca/english/Pgdb/People/Population/demo31c.htm
17. Yoshida E, Ferre E, Barrable B. (1998). Issues in organ procurement: presumed consent, bioethical type II errors, and organ donor registries. *Annals RCPSC.* 31(7):333-335.
18. Moustarah F. (1998). Organ procurement: let's presume consent. *CMAJ.* 158(2):231-234.
19. DePalma J, Townsend R. (1996). Ethical Issues in Organ Donation and Transplantation: are we helping a few at the expense of the many? *Critical Care Nursing Quarterly.* 19:1-9.
20. Stoeckle M. (1993). Issues of transplantation: ethics of potential legislative changes. *Dimensions of critical care nursing* .12(3):158-166.
21. Robertson J. (1999). The Dead Donor Rule. *The Hastings Center Report, November/December.* Pp.6-14.
22. Sytsma S. (1999). Reply to Loewy: Anencephalics and slippery slopes. *Theoretical Medicine and Bioethics.* 20:455-460.
23. Arnold R, Siminoff L, Frader J. (1996). Ethical issues in organ procurement. *Critical Care Clinics.* 12(1):29-48.
24. Agich G. (1999). From Pittsburgh to Cleveland: NHBD Controversies and Bioethics. *Cambridge Quarterly of Healthcare Ethics.* 8:269-274.

ROSS MEMORIAL HOSPITAL

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Forum

Evaluating Financial Supports for Medical Students

Steve Singh, B.Sc. (0T3)

Forum
This section, new to the *UTMJ*, presents a current issue facing the medical community. Following an objective presentation of the issues, individuals involved in the course and resolution of the problem are invited to voice their perspectives. The ultimate aim is to stimulate discussion.

In May 1998, Ontario set a precedent in Canadian post-secondary education with policies deregulating tuition. This gave universities the discretion to set fees for undergraduate training in professional programs, including medicine. Despite students' best efforts, tuition fees have since escalated at a profound rate. Now concerned over the future consequences, the Ontario Medical Association, the provincial government and medical schools have developed support systems to assist students. While there are various "strings" attached to these strategies, the efforts should be acknowledged and made aware to students who may benefit.

The current first year tuition at the University of Toronto stands at $14,000. Only one year ago, the average tuition for first-year Ontario medical students was $10,387. Even this was a steep 108% increase over the preceding 1997 average. For example, at the University of Western Ontario, tuition rose from $5,489 in 1997 to $10,000 in 1998. Many medical graduates can anticipate debt loads of nearly $100,000 by the time they enter practice.

This brings to question why an undergraduate student would pursue the challenge of applying to medical school in the first place? In a University of Ottawa survey, 27% of medical students said that annual tuition fees of $10,000 a year would have deterred them from entering medicine had they been aware of such costs. A survey at UWO showed that the proportion of students whose parents earned $60,000 or less fell from 40% to 27% when tuition doubled in 1998.

To the detriment of the medical profession, talented undergraduates may choose other career paths, viewing a medical degree as unaffordable. It is also feared that students will soon enter medicine based on their ability to pay rather than their potential to become good physicians. Medical education in Canada has traditionally been relatively affordable and accessible to individuals from a wide range of socioeconomic and ethnic groups who later serve an equally diverse population. High tuition fees may close this door for some.

Once in medical school, the predicted consequence of high tuition fees is a resulting "brain drain" in two respects: (1) A pull to the U.S. or large urban Canadian centers to maximize earning potential, and (2) students seeking specialties with the shortest training or highest earning potential, in order to pay off debts quickly. These consequences may result in shortages in rural and/or under-serviced areas and specialties already faced with staffing problems.

The Canadian Medical Association position paper on this issue[1] recommends: (1) increased government funding, (2) regulated and reasonable tuition increases by universities, and (3) financial support systems developed to meet the needs of medical students.

Hence the OMA developed the Ontario Medical Student Bursary Fund earlier this year. Originally chaired by Dr Albert Schumacher, the present OMA president, the sources of the funds are the Ontario Medical Foundation, MD Management and corporate donations. Directed within the medical community, they also solicit various Ontario physicians for a tax-deductible contribution of up to $150 quarterly over 5 years ($3,000 in total). It is designed to provide a minimum of $2,000 to medical students in financial need, a criterion estimated to be met by a third of Ontario's medical students.

The provincial government is also following an election promise to provide tuition assistance to medical students willing to relocate to under-serviced areas. Four million dollars are now available in tuition grants and incentives to help alleviate chronic shortages of physicians in areas of Ontario. Medical students will be eligible for a $10,000 per year grant for a minimum of 3 years and maximum of 4 years. In return, a year of service in an under-serviced area is required for each year of assistance received. This offer is not open to first-year undergraduate medical students, who are more likely undecided as to where they would like to practice in 6 to 10 years time, and thus asking for a commitment from them was deemed unfair.

Many argue that this system is not a long-term solution to the problem of physician shortages. It is also seen as a "tied aid" package

However, it is an effort by the government to recog- potential disaster in the delivery of health care services in and attempt to remedy it.

increases have become a reality to which student opposi- has had limited impact. Instead, the success of their lobbying may be in the creation of financial supports that enable students to cope with these changes. Stipulations attached to these programs may be considered unfair to some. Yet, those not sharing this view will undoubtedly benefit by being able to continue their studies and build a rewarding career practicing medicine.

References

1. Canadian Medical Association. (2000). CMA position paper: Tuition fee escalation and deregulation in undergraduate programs in medicine. Website: http://www.cma.ca/advocacy/tuition/position_paper.htm
2. Canadian Medical Association. (2000). Ontario MDs asked to support financially strapped medical students. Website: http://www.cma.ca/cmaj/cmaj_today/02_24.htm

A Response from the Provincial Government of Ontario

The Honorable Dianne Cunningham,
Minister of Training, Colleges and Universities

The Ontario government is committed to two key priorities in the postseeondary education system: ensuring every willing and qualified student has aceess to high quality and relevant education programs; and ensuring the system is responsive to the needs of our communities.

To meet these commitments, we recently announeed the largest capital program in 30 years that will see the creation of 73,000 new student spaees in our eolleges and universities. We have also introduced a number of initiatives to increase the supply of critical professionals in the health care and education systems.

We are firmly committed to ensuring that Ontario's universities have adequate funding to offer a quality education. These costs must be shared appropriately by students and taxpayers. Beginning in 1996-97 universities were allowed greater discretion in fee setting to ensure they had the resources to maintain a leadership position in professional fields. However, where fees were deregulated, institutions were required to set-aside 30 per eent of the increase to help students in financial need. The remaining 70 per cent of the additional revenue is to be allocated to improve the quality of the students' programs and for investing in additional edueational program improvements.

In the area of healtheare, this government believes people must have access to high quality services wherever they live in Ontario and that an appropriate supply of physieians and other medical professionals is crueial to maintaining a high standard of patient care throughout the province. The Ontario government is investing almost $1 million to add 40 new undergraduate positions at the province's five medieal sehools this fall. In addition, we will invest $22.6 million to ensure capacity for 2,000 students to graduate from the new four-year baccalaureate degree in nursing by 2005. These programs will be offered collaboratively by colleges and universities.

As part of our government's continued commitment to improving access to health care services, we are carrying out our promise in the Blueprint and the Budget 2000 to offer tuition grants to medical students willing to practiee in an underserviced area. In exchange for agreeing to practise medicine in a designated underserviced area for a minimum of three years, medical students will receive $10,000 for each year of undergraduate medieal training. Undergraduate medical students in their last year of medical school and postgraduate medical students will be able to apply to the program.

With these and other policies, the Ontario government is shaping a health and edueation system that is responsive to the needs of the people of Ontario.

A Response from the University of Toronto Medical Alumni Association

Jay Keystone, M.D., President

"No student will have to discontinue his/her studies beeause of financial need". This bold promise by former University of Toronto President, Rob Prichard, was a welcome response to those who questioned the dramatic increase in tuition fees at our great University. However, since the statement applied only to those already enrolled in university programs, it did not address the impaet that increased tuition would have on the demographies of applicants to our medical school and on the future provision of health care in our province.

It doesn't take the financial wizardry of former Dean Aberman (not to say that Dean Naylor isn't savvy in this regard) to figure out that tuition of $14,000 per year will be a prohibitive faetor for students from lower income families to apply to medieal school. These are the very students, from rural areas and varied backgrounds, that we want in our medical schools, to become a physician population that represents a range of socioeeonomic and cultural groups which ean best serve the needs of our diverse communities. Furthermore, as Steve Singh pointed out above, medical students entering residency programs with $80-$100,000 of debt are most likely to seek out the shortest or most lucrative routes to licensure and subsequent debt relief. This may have an additional impaet on the provision of health eare in our province.

And, what has our provincial government and the Ontario Medical Association done to assist our students in their neediest hours? The Ontario Government, almost wholly responsible for this nightmare when it cut educational funding, is now "bribing" our students through a return-of-service program to encourage them to relocate to under-servieed areas. What the Ministry has failed to mention is that historieally return-of-service programs do not work, and are most unsatisfactory for those who are served by them. Nice try — but no cigar!

On the other hand, the OMA has instituted a highly publieized campaign (the Ontario Medieal Bursary Fund), to raise money for Ontario medical students by solieiting funds from Ontario physieians who graduated out of province (the least likely to respond) and by utilizing Medical Alumni Association fund raising eampaigns from all 5 provincial universities. Unfortunately, at the University of Toronto, the impaet of such a campaign will almost eertainly be a significant reduction in funds available to support student activities, such as our Undergraduate International Health Program, summer researeh scholarships, and innovative extracurricular programs through our newly formed partnership with the Offiee of Student Affairs. Worrisome!

Finally, what are we at the MAA doing to provide financial assistance in these difficult times? We have, after much deliberation, joined the OMA Bursary Fund campaign on the understanding that we will endeavor to raise money for bursaries while attempting to maintain our financial support of student programs and activities. Through the outstanding support of our medical alumni, the OMA recently raised nearly $60,000 in bursary support from approximately 90 generous donors; these results were achieved during a pilot project in which only 250 alumni were contacted. Also, we have created a large endowment for interest-free loans, and thanks to a significant contribution from the Kurdyak family, will be able to further increase our loans this year. Do remember that our loan repayment policy is extremely generous! In addition, through a close collaboration with the Faculty of Medicine Development Office, the MAA is in the process of increasing its fund-raising capability, with the aim of generating additional revenue for student aid. As well, the Faculty has established student support as a fundraising priority.

Not unlike Rob Prichard, the Medical Alumni Association has made a promise of its own: "To oppose any tuition increases so that applicants to our great medical school will be accepted on the basis of merit, not on their ability to pay."

A Response from the Medical Student

Irfan Dhalla, B.A.Sc. (0T3), Second Year Medical Student, University of Toronto

A decade ago, a first-year medical student at the University of Toronto paid $2,084 for a year's tuition and could look forward to receiving $5,172 as a stipend during clerkship. Today, a first-year medical student at U of T pays $14,000 in tuition and receives no compensation for the countless nights and weekends spent on-call. Is it any wonder that more Canadian students than ever are writing the United States Medical Licensing Exam?

Tuition is not the only expense facing medical students. Like everyone else, medical students need shelter, food, clothing and transportation. Unique to medical students are outlays for travel to clinical electives and residency interviews. Yet between the Canada Student Loan and the Ontario Student Loan, medical students can borrow just $11,000 per year. Obviously this is insufficient for many students.

The Ontario government has recently been trumpeting a program claimed to provide 'free tuition' to medical students willing to practice in underserviced areas. By offering up to $10,000 for every year of service (a figure that is less than tuition at most Ontario medical schools), the government believes it is improving medical school accessibility and increasing physician supply in rural Ontario. The first claim is hypocritical, since the government allowed tuition to skyrocket in the first place. And the second claim is a fantasy – for years the Canadian military has had trouble signing up recruits for its far more lucrative return of service plan. Some students will benefit from the government's offer, but the majority of those who sign up would have chosen to practice in underserviced areas anyway.

Although student lobbying has not been effective in halting medical student tuition increases, some efforts have been moderately successful. Residency tuition at the University of Toronto was staved off for a year and then dropped entirely. Due in large part to a massive student-led campaign, medical student tuition at the University of Western Ontario has been frozen for two years. Two years ago, medical students asked the Ontario Medical Association to launch a bursary fund, and the OMA, in partnership with the medical schools, is doing so. At U of T, the Medical Alumni Association has responded to increased student need by ramping up its student aid programs.

Earlier this year, the Ontario Medical Association attempted to negotiate a clerkship stipend on medical students' behalf, and though that effort failed, a new program to provide $1,500 per month for students on rural electives was the result. Program details are still being worked out, but this program should ensure that medical students who want to experience rural medicine will be able to do so at little or no cost.

The many programs being put in place are much needed, but they do not directly address the fundamental issue of increasing barriers to post-secondary education. Ultimately, we as a society need to answer a simple question. Do we believe that a medical education should be paid for up front, and therefore made relatively inaccessible to the poor, or do we believe that education should be paid for mostly through taxes, after graduates have begun reaping the fruits of their labour?

A Response from the Ontario Medical Association

Albert Schumacher, M.D., President

Tuition increases without available financial support will ultimately change the face of those who practice medicine in this province. The medical care system needs individuals from different socio-economic, cultural, rural and urban backgrounds to serve an equally diverse population of patients. The OMA firmly believes it is in society's interest to ensure that medicine remains a rewarding and affordable career accessible to students based on their passion and academic performance, not their financial status.

The Ontario government's plan to offer medical students tuition grants to work in underserviced areas will not significantly address the serious problem of physician shortage. According to Ontario's medical students, one long-term solution is to cap escalating tuition fees, which government deregulated. Programs to teach medical students about rural medicine and increase placements in these areas are essential. And there must be an increase in medical school enrolment to train physicians to care for an aging and growing population."

Although results to date are promising, the Ontario Medical Student Bursary Fund requires continued support and participation from physicians to be successful enough to make a significant difference to financially challenged medical students today and in the future. So far, the OMSBF has reached nearly half of its $4 million goal. Future fund raising initiatives will include contacting all non-Ontario physician graduates for their support, developing an annual campaign to accommodate the large number of one-time gifts received, and approaching corporations and foundations for their financial support.

The Young Golfer's Swollen Leg

Section heads: Martin C. Chang, Ph.D. (OT3); Catherine Chung, B.Sc. (OT3)

Introducing Morning Report

"Morning Report" is a tradition at the University of Toronto, and indeed of most internal medicine training programs. Morning Report facilitates teaching and learning at various levels of medical training, promotes social interaction between the medical faculty and the medical housestaff, and fosters discussion of issues related to local hospital operation. Although the specific format and approaches vary, typically a clinical case is discussed in a group setting with varying instructive goals in mind. Traditionally, the medical staff that was on-call the night before presents a case from the previous day's admissions. A staff physician then leads a discussion emphasizing the clinical reasoning process involved in the diagnosis and management of the patient's condition. Discussion highlights the generation of a provisional and differential diagnosis based on the information at hand, and how hypotheses are modified with additional information, including laboratory and radiological findings. The management of the patient's condition is also discussed. Morning Report in the *UTMJ* is a solitaire version of this group discussion and you, the reader, are encouraged to formulate your own hypotheses. We recommend a pause after each case presentation to consider the issues you feel are important before continuing with the discussion.

Case Presentation

Cody is an 18-year-old high-school senior from Sarnia, Ontario who was set to go to South Carolina for a summer golf tournament. Sitting in the car on the way to the tournament, he noticed some discomfort, but once he arrived, he was able to golf for two days. On the third day, he began to feel generally fatigued and ill, and had aches in his shoulders and right hip, which affected his golf swing. By the end of the day, his right leg became very swollen from the calf, past the knee to the lower thigh. His malaise was such that he had to be put on a bus back home that evening. He was able to see a family doctor at a Sarnia clinic in the morning.

Discussion

What might be causing the swelling in Cody's leg?

In a young active patient, local trauma is common, although during Morning Report one is often reminded that a case of trauma rarely requires the services of Internal Medicine. In general, swelling in one leg could result from venous obstruction or lymphatic obstruction. Obstruction in general could be caused by local inflammation, such as occurs with cellulitis, or erythema nodosum (inflammation of the deep dermis and fat causing red nodular swelling). Local or metastatic neoplasms could also cause obstruction; in Cody's case (a young male) one might suspect testicular cancer.

Another common cause of venous obstruction is thrombosis. (Lymphatic obstruction, which classically causes non-pitting edema, is less common). Cody was in fact found to have deep-vein thrombosis (DVT) of the right superior femoral and popliteal veins. DVT can have a number of underlying etiologies, many of which will require further investigation.

What factors predispose to DVT?

Predisposing factors form "Virchow's triad": venous stasis, hypercoagulability, and endothelial damage. Venous stasis can result from limb immobility, right-heart failure, and previous obstructions. Hypercoagulability can result from numerous conditions, including malignant tumours, high estrogen states, and a variety of acquired or inherited conditions relating to components of the clotting cascade. Damage to endothelial cells can be caused by infection, vasculitis, and trauma. Note that these causes are not mutually exclusive; indeed, one can predispose to another.[1]

Case Presentation

Cody's complaints had actually begun three weeks ago, when he was treated for sinusitis. He was complaining of sinus congestion and, on blowing his nose, produced a purulent yellow discharge flecked with blood. He was prescribed clarithromycin, which was subsequently changed to levofloxacin. A week later, he presented with cough, producing yellow sputum with spots of blood. His coughing paroxysms occasionally led to retching and vomiting. His treatment was changed to steroidal inhalers and azithromycin, and he felt well enough to travel a week later. When he arrived at the clinic the day after his bus ride home from the golf tournament, Cody was still feeling unwell. His cough had returned, and his right leg was very swollen and sore. His medical history is otherwise unremarkable. On examination, his temperature was 38.3°C, and he had an erythematous rash on the lower right side of his neck. There was increased dullness to percussion in the lower fields of both lungs. His physician ordered chest X-rays and laboratory investigations.

Discussion

What are the causes of sinusitis?

Sinusitis refers to inflammation of the paranasal sinuses due to infection (bacterial, viral, or fungal) or allergic/autoimmune reactions. Common infectious agents include streptococci or pneumococci, *Haemophilus influenzae,* staphylococci, and some anaerobic bacteria.

What is the differential diagnosis for cough?

The differential diagnosis for cough is wide ranging, and can be roughly divided into several categories: aspiration of foreign substances, airway disease, parenchymal disease, cardiac, and drug-induced causes. Diaphragmatic irritation from abdominal sources can also cause cough. Important airway diseases include chronic/acute bronchitis, asthma, COPD, and bronchiectasis, whereas important parenchymal diseases include pneumonia, pulmonary embolism, lung/metastatic cancer, lung abscess, and interstitial disease. Pneumonia itself can be caused by a number of infectious agents: bacterial, viral, and other.[2] Antibiotics were prescribed since Cody's productive cough and history of nasal discharge were consistent with a bacterial pneumonia, secondary to his earlier sinusitis (*i.e.*, a common infectious cause).

Are there any diagnoses unifying Cody's DVT and respiratory symptoms?

Pulmonary embolism, mentioned above, can be a consequence of DVT. Metastatic cancer remains a possibility, although it would be difficult to make a diagnosis without further investigation. Also possible are vascular and immunologic conditions such as sarcoidosis, Goodpasture's, systematic lupus erythematosis (SLE), and the vasculitis syndromes. Although these conditions often have unclear etiologies, they are all multisystem disorders with vascular involvement that predispose to pulmonary inflammation.

Case Presentation

The chest X-ray will be examined in the next section. Results of the tests on Cody's blood are as follows (normal values are in parentheses):

Table 1
Blood Lab Results

Hemoglobin	95 g/L (140)	Na^+	132 mM (140)
MCV	86 fL (80-95)	K^+	5.6 mM (3-5)
WBC	11.5 x 10^9/L (3.8-10.8)	Cl^-	93 mM (95-108)
Platelets	405 x 10^9/L	HCO_3^-	24 mM (22-29)
ALT, AST	Normal	Creatinine	623 µM (<106)
Bilirubin	Normal	BUN	28.2 mM (2.5-10.7)
Serum glucose	6.7 mM (4-7)	Albumin	28 g/L (35-50)

Discussion

Which results are the most significant?

Regardless of clinical presentation, hyperkalemia (plasma $K^+ > 5$ mM) is always a key concern due to the cardiac toxicity of potassium. ECG abnormalities can be seen with plasma $K^+ > 5.5$, and arrhythmias with plasma $K^+ > 6.5$. Based on the plasma creatinine and blood urea nitrogen, Cody has significantly compromised glomerular filtration. A urinalysis subsequently showed "active" urinary sedimentation suggestive of inflammation of the glomerulus, or glomerulonephritis (GN).

What conditions are associated with glomerulonephritis?

This has a wide differential diagnosis. The GN could be post- or peri-infectious, occurring due to immune-complex deposition. One must also consider collagen-vascular diseases (*e.g.* polyarteritis, SLE, and Wegener's granulomatosis), cryoglobulinemia, and anti basement-membrane diseases (*e.g.* Alport's and Goodpasture's). The gold standard for distinguishing between these etiologies is renal biopsy with fluorescence microscopy. Nevertheless, serology for immunological factors, combined with an understanding of the different multisystem manifestations of the disease, will provide high diagnostic confidence.[3]

Case Presentation

Cody was admitted to the Toronto General Hospital for management and treatment of his kidney failure, and a CT scan of his chest. The chest X-ray (Figure 1) showed a diffuse distribution of nodular lesions. CT scans showed nodular densities throughout the lung. An example, taken inferior to the hilum, is seen in Figure 2. Another example is shown in Figure 3; the arrow indicates a cavity within one of the lung lesions, consistent with granulomatous inflammation.

Figure 1. *Chest X-ray*
AP view of Cody's chest shows a diffuse distribution of nodular lesions.

Discussion

What disease process causes nodular lesions in the lung?

Although biopsy results are not yet available (as is typical during Morning Report), the nodular lesions in the lung are typical of necrotizing granulomatous inflammation. These granulomas consist mostly of loosely arranged macrophages. These professional phagocytic cells take over a week to infiltrate and activate, in contrast to the acute action of neutrophils. Once they are present in

Figure 2. *CT Scan*
Transverse section, taken inferior to the hilum, shows several nodular densities which were present at all levels of both lungs.

Figure 3. *CT scan showing a cavitary lesion (see text).*

significant numbers, macrophages will intercalcate in complex patterns resembling epithelial cells. Such "epitheloid" macrophages form a sheet of cells to enclose areas of inflammation, hence the nodular appearance of the lesions. Large areas of necrosis, followed by apoptosis of the infiltrating cells, will be visible on a chest X-ray as cavitating lesions.[2] The differential diagnosis for granulomatous inflammation includes persistent mycobacterial infection (*e.g.*, tuberculosis, leprosy), fungal or parasitic infections, beryllium toxicity, hypersensitivity to inhaled irritants, and autoimmune diseases such as rheumatoid arthritis and Wegener's granulomatosis.

What is the diagnosis?

Serology for erythrocyte sedimentation and anti-neutrophil cytoplasmic antibodies (ANCA) showed positive ESR and c-ANCA levels, and Cody was given a presumptive diagnosis of Wegener's granulomatosis. The complete Wegener's triad was present: aseptic necrotizing vasculitis of the lung and upper respiratory tract, and GN in the kidney. A definitive diagnosis will require biopsy and visualization of the lung lesions.

Wegener's is a rare, potentially fatal disease of suspected immunological origin, although the precise etiology is unknown. It occurs equally among males and females, but more frequently in middle age and less frequently in populations of African origin. Like other vasculitis syndromes, Wegener's can manifest itself in virtually any vascular tissue, including endothelial inflammation in the peripheral veins, seen in Cody under the guise of DVT. As in this case, non-specific symptoms often associated with inflammation are often seen: fatigue, fever, nausea, arthralgias, malaise, etc.[3]

Serology is important given that >90% of confirmed Wegener's patients have high c-ANCA titres, with normal p-ANCA and ANCA.[3] Further confirmation could be obtained through biopsy of lung tissue, looking particularly for granulomatous vasculitis. Based on clinical signs alone, other multisystem diseases that could appear Wegenerian include microscopic polyangiitis (lacks granulomatous lesions), Goodpasture's syndrome (low ANCA, high anti-glomerular basement membrane anibodies), Churg-Strauss syndrome (eosinophilia, p-ANCAs), infection, sarcoidosis, and lymphoid granulomatosis (atypical lesion composition).

Conclusion

Cody was treated with oral cyclophosphamide, an immunosuppresant, with some glucocorticoids for relief of the inflammatory symptoms. Within two weeks, Cody was feeling better, with the Wegener's in remission. The cyclophosphamide will be continued for a year, titrated with close monitoring of leukocyte levels to prevent leukopenia. The glucocorticoids will be continued for six months, and both drugs will gradually be tapered at the end of the course. There is a good chance that Cody will be able to participate fully in the next golf season.

Acknowledgements

The authors are indebted to Dr. Kevin Katz, currently Chief Resident at Toronto General Hospital for his generous encouragement and insightful suggestions. Diagnostic images were selected by Dr. Gord Weisbrod, a radiologist at Toronto General Hospital.

Clinical Pearls

- The chief complaint is not always central to the diagnosis.
- When faced with multiple and varied clinical symptoms, look for unifying diagnoses.
- Wegener's granulomatosis is diagnosed using a combination of Wegener's clinical triad, serology, and tissue biopsy.

References

1. Moore S. (1996). Vascular System. In: *Anderson's Pathology, 10th ed.* Damjanov I and Linder J (eds). Mosby.
2. Kuhn CK III, West WW, Craighead JE, and Gibbs AR. (1996). Lungs. In: *Anderson's Pathology, 10th ed.* Damjanov I and Linder J (eds). Mosby.
3. Pauci F. (1999). Vasculitis Syndromes. In: *Harrison's Textbook of Internal Medicine, 14th ed.*

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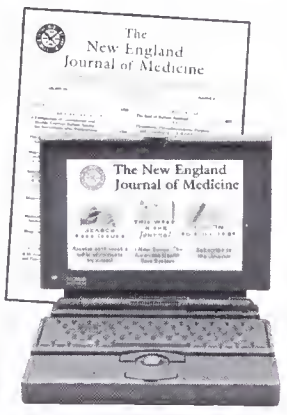

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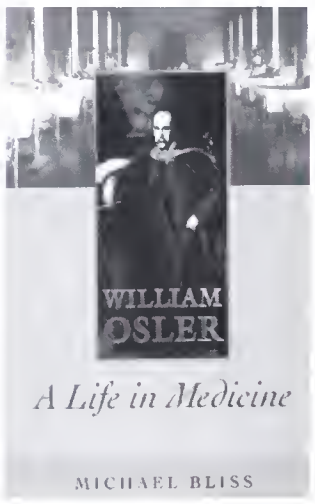

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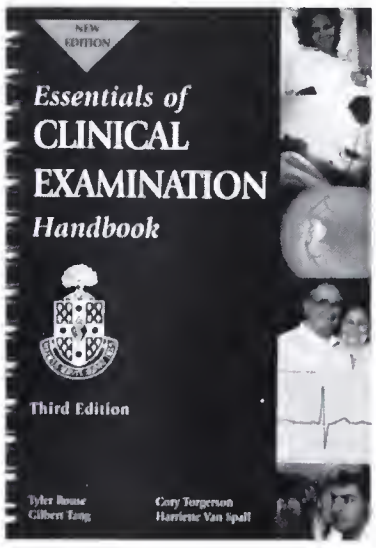

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Case Reports from the University of Toronto Faculty of Medicine

Piero Tartaro, B.Sc. (OT3), Steven W.H. Hwang, B.Sc. (OT3)

Case 1

Stanley Fenton, M.D., F.R.C.P. (I)
Division of Internal Medicine, Toronto General Hospital

A 40-year-old male on hemodialysis due to end-stage renal disease (ESRD) presents to the hospital with left flank pain and hematuria. His ESRD is secondary to a kidney disease diagnosed in his teens; his father, uncle, all 5 of his siblings, and his paternal grandparents were all afflicted with the same disease. The family history also revealed that his father and uncle both had intracranial aneurysms, the former having died from this event. Previous CT scans and ultrasounds demonstrated the presence of multiple cysts throughout the cortex and medulla of both kidneys (Figure 1.1).

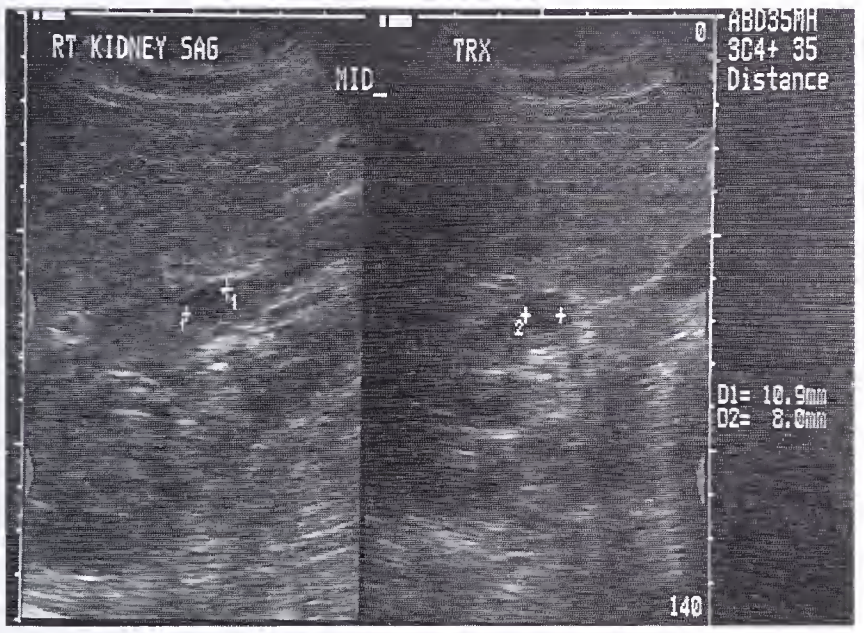

Figure 1.1. *Ultrasound of right kidney showing multiple cysts.*

What is the kidney disease diagnosed in his teens?

What is the most likely cause of the pain and hematuria, and what is the significance of the family history of intracranial aneurysms?

Case 2

Vincent Chien, M.D., F.R.C.P.(C)
Division of Medicine, Saint-Michael's Hospital

A 34 year old female arrives at the hospital complaining of stuttering speech, "shaking of limbs", worsening difficulty walking, and having had a 5 minute seizure. The history reveals that 7 years ago, she began experiencing vague, generalized numbness, occasional "electric shocks", and light-headedness. Family history suggests that her mother passed away at the age of 42 of a rapidly progressive dementia. MRI scan and EPs of the patient taken 7 years ago showed no significant abnormalities. Upon further investigation, you note that she has had rapid memory loss (poor recall, no new memories, poor distant memory recall). She scores a 20/30 on her mini-mental test and her EEG is shown below (Figure 2.1).

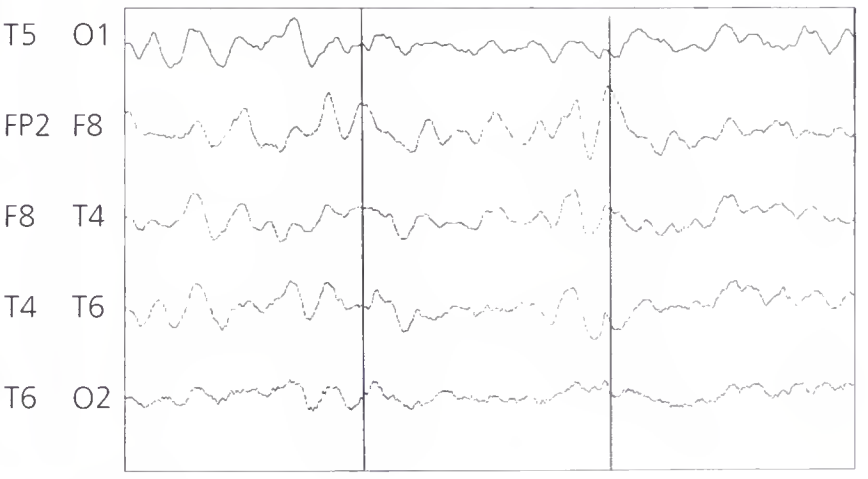

Figure 2.1. *EEG*

What is the diagnosis?

What other tests would you order?

Case 3

[illegible] Salit, M.D., C.M., F.R.C.P.(C)
[illegible] of Infectious Diseases, Toronto General Hospital

A 69 year-old, HIV-positive man presents with soreness in the left hip. For over six months, he has been experiencing a grumbling, aching pain in his left hip that occurs mainly on climbing stairs, with prolonged walking, and at night. Recently, these symptoms have begun to appear in the right hip as well. Physical examination reveals limited range of motion of the left hip with significant flexion contracture and flexion to just beyond 90 degrees. There is almost no rotational movement present and abduction is only about 20 degrees. There is little diminution of rotational movements for the right hip. X-rays of his left hip were taken (see Figures 3.1 and 3.2). Past medical history reveals that he suffered an episode of pneumocystis pneumonia two years prior, for which he was given a prolonged course of steroids. He was on antiretroviral therapy with an excellent antiviral and immunologic response.

Figure 3.1.
X-ray of left hip.

Figure 3.2.
X-ray of left hip

What is the diagnosis?

What is the most likely cause?

Case 4

Susan M. Tarlo, M.B., B.S., F.R.C.P.(C)
Division of Respirology, Toronto Western Hospital

A 44 year-old, non-smoking man complains of feeling unwell with flu-like symptoms. He has had a fever of 40°C and has been experiencing night sweats as well as chills, rigors, and myalgias for the past 4 weeks. Over the last couple of weeks he has also experienced weight loss and feels lethargic. The antibiotics prescribed to him 4 weeks ago have not shown any improvement in his condition. Upon interviewing the patient, you realize that he developed his illness days after returning from a trip to Costa Rica where as a geologist he was investigating a cave which housed many bats; several other expedition members have also fallen ill. Initial chest X-rays 4 weeks ago were clear and recent X-rays are as shown (Figure 4.1 and 4.2). His hemoglobin level is 123 g/L and pulmonary function tests only display the following abnormal results: VC 36% of predicted; FEV1 32% predicted; and DCO 40%. He has no crackles or wheezing and his family history does not prove significant.

Figure 4.1.
PA chest x-ray.

Figure 4.2.
Lateral chest x-ray.

What is the likely diagnosis?

What treatment is required?

Case 5

Irving Salit, M.D, C.M., F.R.C.P.(C)
Division of Infectious Diseases, Toronto General Hospital

Mr. and Mrs. A are a Vietnamese couple who had resided in a refugee camp. Mrs. A had aching in her wrist, so she visited a doctor who prescribed herbal medications. He crushed some plants, created a slurry and injected part of the mixture subcutaneously into Mrs. A's wrist. Mr. A had accompanied his wife to the doctor and indicated that he had a sore lower back; this prompted the doctor to inject some of this plant material into Mr. A's back. Approximately two weeks later, Mr. and Mrs. A both noted tender nodules at the site of the injections. Over the ensuing weeks, these nodules spread to such an extent that Mrs. A had numerous nodules that had marched up her arm (Figure 5.1). Mr. A had a cluster of nodules at the injection site on his back (Figure 5.2). Aspiration of one of the suppurative nodules from Mrs. A revealed the causative organism: *Sporothrix schenckii*.

What is the diagnosis?

Figure 5.1. *Nodules on arm of Mrs. A*

Figure 5.2. *Nodules on back of Mr. A*

Case 6

Irving Salit, M.D., C.M., F.R.C.P.(C)
Division of Infectious Diseases, Toronto General Hospital

A 27-year-old man presents with left ankle pain which began several months prior and has become increasingly red and painful. X-rays taken one month prior for right-sided chest pain showed a pleural-based mass in the right upper lobe. Over the past 10 days, he has been experiencing a dry cough, especially early in the morning and late in the evening. He denied any fever, chills, sweating or weight change. There was decreased air entry and dullness to percussion in the right upper lobe. There was no hepatosplenomegaly and no lymphadenopathy. The ankle was swollen and appeared reddish-purple; pus was noticed at the site from which a skin biopsy had been taken (Figure 6.1). The social history revealed that he was born and raised in Vietnam and moved to Canada in 1991. Besides a return visit to Vietnam for two months in 1993, there is no other significant travel.

What is the diagnosis?

Figure 6.1. *Area of redness and pain on ankle prior to treatment*

Case 7

Jenny Heathcote, M.B., B.S., M.D., F.R.C.P., F.R.C.P.(C)
Division of Gastroenterology, Toronto Western Hospital

A 62-year-old man presents with fatigue, ankle swelling, and shortness of breath. Over the last 10 years, he has noticed an intermittent red rash on his lower legs which fades and leaves brown blotches around his ankles (Figure 7.1). He had been tattooed as a youngster, was a past IV drug user, and had a history of drinking 5 beers a night. On examination, the chest was clear and his JVP was 3 cm. The abdominal exam revealed a firm liver and hepatomegaly (14 cm span). A spleen tip was also palpable. There was no ascites but he had pitting edema to the mid-calf.

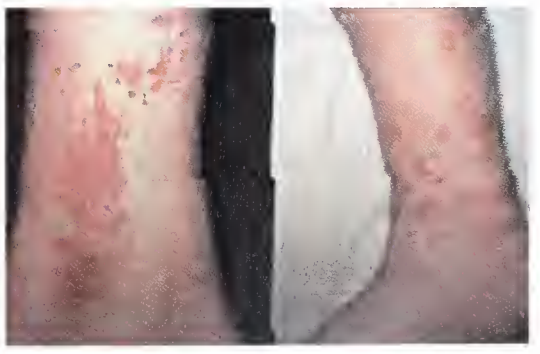

Figure 7.1. *Lower leg rash*

Laboratory tests showed a mild pancytopenia (Hb 110 g/L; WBC 2.8×10^6/L; platelet count 93×10^9/L). His serum aminotransferases were mildly elevated, and his bilirubin was normal, but the serum albumin was low at 26 g/L. His blood urea and creatinine levels were normal. However, he was found to have proteinurea which measured 4gm/24 hours.

What is the diagnosis?

And the diagnosis is...

Case 1

Diagnosis: Autosomal dominant polycystic kidney disease

[redacted] has autosomal dominant polycystic kidney disease (ADPKD). It affects approximately 1 of every 300 to 1000 live births and accounts for approximately 10% of end-stage renal disease. Mutations in three genes have been implicated in the pathogenesis of ADPKD: PKD1 which encodes for the protein polycystin 1, PKD2, which encodes for the protein polycystin 2, and PKD3, which has yet to be mapped. These proteins are believed to play a role in cell-cell matrix interactions important in tubular epithelial cell growth and differentiation. The kidneys of an ADPKD patient are grossly enlarged with multiple cysts throughout both the cortex and medulla. In contrast to the present case, the disease is usually asymptomatic until the third or fourth decade, at which time signs and symptoms appear that are usually related to effects of the cysts (*e.g.*, lumbar discomfort/pain, hematuria, UTI, colic due to kidney stones) or to a loss of renal function. Chronic flank pain is normally due to the mass effect of the enlarged kidney; however, acute flank pain indicates infection, urinary tract obstruction, or sudden hemorrhage into a cyst. This patient was experiencing hematuria due to uncontrollable bleeding of a renal cyst in the left kidney. A left nephrectomy was performed, and years later, similar symptoms led to a right nephrectomy. Since intracranial aneurysms are associated with ADPKD, the family history of intracranial aneurysms warranted an MRI angiography when this patient experienced recurring headaches. The MRI did not detect an aneurysm. The association of intracranial aneurysms, as well as aortic root dilation, with ADPKD may represent altered expression and function of the PKD gene in arterial smooth muscle and myofibroblasts.

Case 2

Diagnosis: Creutzfeld-Jakob Disease (CJD) or subacute spongiform encephalopathy

CJD is believed to be transmitted by distinctive proteins, prions, which fold normal proteins into abnormal states leading to pathology. Common symptoms are rapidly progressing dementia, myoclonic jerks and extrapyramidal symptoms. The only confirmatory diagnostic test is a pathological biopsy, but MRI and EEG have proven useful in diagnosing many cases. The MRIs commonly show frontopyramidal, occipitoparietal, and/or cerebral cortical with basal ganglia (including thalamic, midbrain cerebellar, or spinal) involvement. EEGs may show a pattern of periodic sharp wave complexes (PSWC) as seen in Figure 2.1.

Figure 2.2. *T1-weighted MRI.*

Therefore other tests to confirm the diagnosis would include an MRI (as shown in Figure 2.2) and a CSF protein marker test. Her MRI shows slightly increased activity below the inner caudate, anterior thalamus, frontal, temporal, and occipital lobes. A protein marker 14-3-3 has also been associated to CJD and can be tested via spinal fluid. The history and tests are highly suggestive of a familial variant of CJD.

Case 3

Diagnosis: Avascular necrosis of the femoral head

Pathological changes in avascular necrosis (also known as osteonecrosis) are characterized by cell death in bone resulting from compromised blood supply, the magnitude of necrosis being a function of the degree of circulatory compromise. In this case, the most likely cause is the high dose of steroids this patient received for treatment of his pneumonia. Table 1 lists the disorders associated with avascular necrosis.

The X-rays confirmed that this man had stage III to IV avascular necrosis of the femoral head with collapse of the wedge-shaped zone that encompasses virtually all of the weight-bearing surface as well as some underlying cyst formation and some early acetabular changes. He received a total hip arthroplasty that allowed him to regain a reasonable range of motion in his left hip. He was given Celebrex to help with his right hip but, due to progressive deterioration, another total hip arthroplasty was required.

Table 1
Disorders associated with avascular necrosis

- Idiopathic
- Corticosteroid administration
- Dysbarism
- Connective tissue disorders
- Gaucher disease
- Alcohol abuse
- Tumors
- Trauma
- Infection
- Radiation therapy
- Pregnancy
- Sickle cell and other anemias
- Chronic pancreatitis
- Epiphyseal disorders

Case 4

Diagnosis: Histoplasmosis

Histoplasmosis is contracted via a fungus, *Histoplasma capsulatum.* The fungus grows preferentially in moist surface soil or areas with lots of bird or bat feces. Often symptoms appear 5 to 18 days after exposure to *H. capsulatum.* The small spores travel to the alveoli and then begin budding leading to a granulomatous reaction that is identified as caseation necrosis or calcification which may also become disseminated. This is seen as nodules on the x-ray (Figure 4.1 and 4.2). His pulmonary function tests show a typical pattern of restrictive interstitial lung disease conforming to histoplasmosis. The typical presentation includes a cough, fever, malaise, and chest x-ray findings of hilar adenopathy with or without one or more areas of pneumonitis. The more chronic cases often include progression over several months with productive cough, weight loss, and night sweats and chest x-rays reveal uni- or bilateral fibronodular apical infiltrates. Mild, acute pulmonary histoplasmosis generally does not require intervention, but severe cases will require antifungal medication. Chronic patients also receive chemotherapy. Initial intravenous amphotericin or oral itraconazole is administered and continued for 1-2 years with follow-ups until 5 years.

The patient recovered completely with treatment using itraconazole for one year.

Case 5

Diagnosis: Sporotrichosis

Sporotrichosis, the most common type of subcutaneous mycosis, is caused by the fungus *Sporothrix schenckii*. It is a dimorphic fungus, existing as rounded, budding forms (yeast-like) in tissues, but growing like a mold when cultured at room temperature. This fungus lives as a saprophyte on plants in many areas of the world; thus this infection is seen most often in gardeners, farmers, or other workers who come in contact with soil or plants. The organism gains access to the deep layers of skin by traumatic implantation (classically, a rose thorn injury); in this case, it occurred by the injection of the herbal medication. A nearly painless red papule forms at the site of inoculation and, although the infection may be limited to the site of inoculation (plaque sporotrichosis), the most common manifestation is for the infection to spread over several weeks, forming similar nodules along proximal lymphatic channels (lymphangitic sporotrichosis). Infection rarely extends beyond regional lymphatics. A positive culture for *S. schenckii* or direct observation of the fungus by microscopic examination of pus provides the definitive diagnosis. Mr. and Mrs. A were treated with itraconazole with marked improvement over 6 weeks.

Figure 5.3. *Microscopic appearance of Sporothrix schenkii*

Case 6

Diagnosis: Erythema induratum due to disseminated tuberculosis

The skin biopsy showed granulomatous panniculitis (an inflammatory reaction in the subcutaneous fat). Erythema induratum, an uncommon form of panniculitis, is sometimes associated with active TB elsewhere in the body. A biopsy of the right upper lobe and a swab from the swollen ankle grew *Mycobacterium tuberculosis*. A CT scan of the lung showed a pleural-based mass, some probable right upper lobe and apical pulmonary consolidation, and a right subphrenic collection. Drainage from the right subphrenic area produced considerable purulent material which grew *M. tuberculosis*. Samples taken from abscesses in the right buttock and right shoulder also grew *M. tuberculosis*. Laboratory testing revealed a multidrug resistant *M. tuberculosis* and he was put on an 18 month course of multiple antibiotics, including ethambutol, pyrazinamide, and ofloxacin. The erythema induratum resolved on anti-tuberculous therapy (Figure 6.2).

Figure 6.2. *Area of infection on ankle after treatment*

Case 7

Diagnosis: Hepatitis C with cryoglobulinemia and nephrotic syndrome

Hepatitis C is a viral infection transmitted via the blood, most commonly by the use of illicit intravenous drugs. Most individuals remain infected for life but are asymptomatic. Hepatitis C is more likely to cause progressive liver disease in those who consume >50 g of alcohol daily (>3 beers/day). This man had cirrhosis on liver biopsy and his splenic enlargement suggested accompanying portal hypertension. The heavy proteinuria was indicative of nephrotic syndrome in this case secondary to his cryoglobulinemia (cause of the red rash on ankles).

Cryoglobulins are comprised of immunoglobulins produced in large amounts by lymphocytes. In this case it is likely that lymphocyte dysfunction had been initiated by the hepatitis C. The proteins clump in the cold, particularly in small blood vessels (*e.g.* skin, kidney, nerves) where they cause vasculitis. The antiviral and immunoregulatory cytokine, interferon-α, combined with the nucleoside analogue ribavirin is used to treat hepatitis C. This treatment was given to the patient and his proteinuria decreased while his serum albumin increased. The cryoglobulins became undetectable in his blood and his skin rash disappeared. Treatment was given for 1 year, but unfortunately patients tend to relapse shortly after the cessation of therapy.

Ultra*LIGHT*: New Frontiers of Medical Imaging?

Victor Yang, M.A.Sc, (M.D./Ph.D.3), Alex Vitkin, Ph.D., Maggie Gordon, B.Sc., Alvin Mok, Louis Wongkeesong, M.D., Paul Muller, M.D., Norman Marcon, M.D., Sheldon Mintz, M.D., and Brian Wilson, Ph.D.

Introduction

The Ultra*LIGHT* imaging system (see Figure 1) presently being developed at the Ontario Cancer Institute (OCI)/Princess Margaret Hospital (PMH) and Photonics Research Ontario (PRO) is based on the concept of optical coherence tomography (OCT).[1-5] The name Ultra*LIGHT* comes from ultrasound, a mature medical imaging modality. Analogous to ultrasound imaging in which a sound wave is transmitted through soft tissue and the image is formed by observing the reflected sound wave, the Ultra*LIGHT* imaging system transmits light waves through biological tissues and the reflection forms the image (see Figure 2). Because the wavelength of light (0.8~1.3 um) is much shorter than that of sound (50~150 um), the imaging resolution of Ultra*LIGHT* is superior to ultrasound. Conversely, since light waves cannot penetrate biological tissue as well as ultrasound, the imaging depth of all imaging systems based on the OCT technology is limited to approximately 2 millimeters. However, the thickness of the epithelial layer lining much of the body surface and cavities is within the reach of the Ultra*LIGHT* imaging depth.[11] Similarly, the endothelial layer of major blood vessels can also be a target.[10] Therefore, Ultra*LIGHT* can be used in dermatological, endoscopic and intravascular applications. In addition, Ultra*LIGHT* can also be designed to operate in Doppler mode[1-6] and image blood flow as slow as 0.2 millimeters per second (Figure 3) and blood vessels less than 20 micrometers in diameter, thereby approaching the flow speed and geometry of capillary vessels.[7]

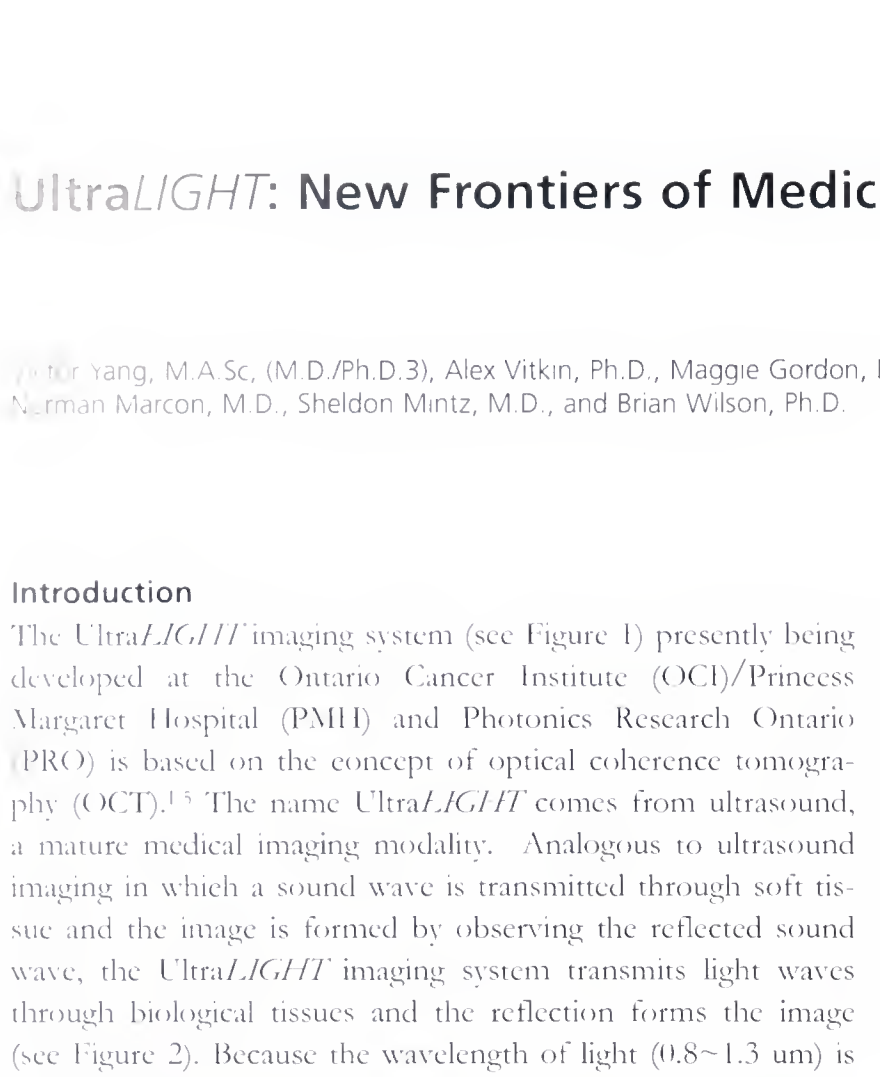

Figure 1. *UltraLIGHT imaging system.*

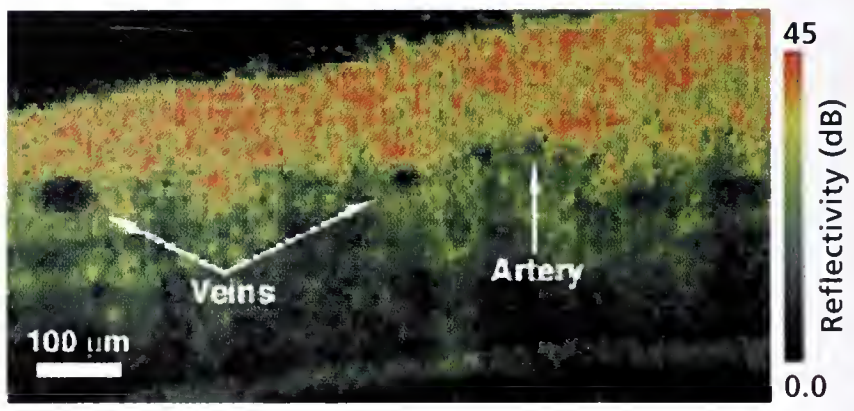

Figure 2. *Cross-sectional OCT image of rodent skin showing microstructures. (Courtesy of Dr. Chen, UC Irvine).*

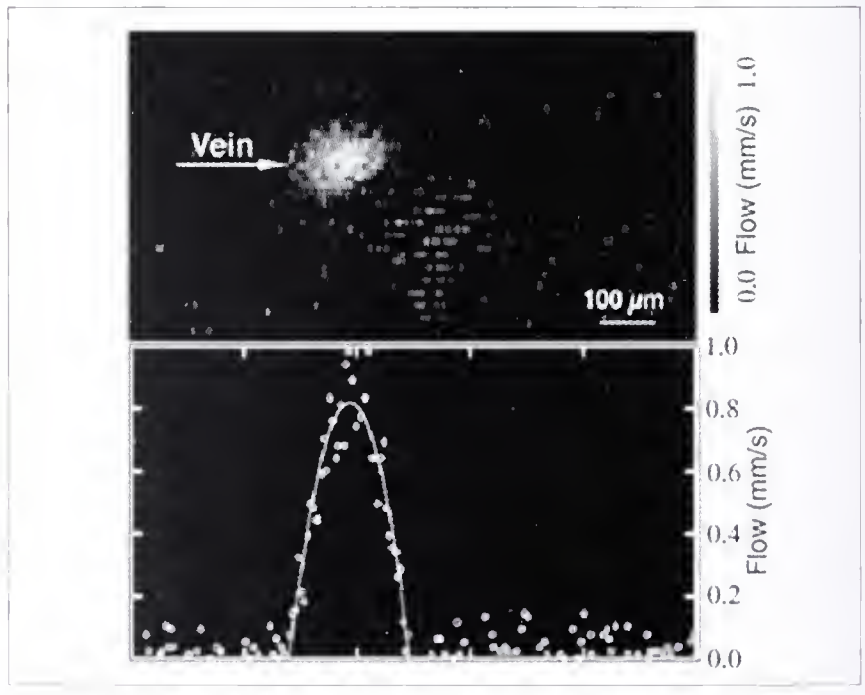

Figure 3. *Doppler imaging of flow using OCT. (Top) Velocity image of venous blood flow; (Bottom) Velocity profile along the diameter of the vein, where the circles are experimental data points and the solid line is a parabolic fit. (Courtesy of Dr. Chen, UC Irvine).*

Technical Background

Although the optical coherence tomography technology is analogous to ultrasound, it operates on a faster time scale as the speed of light is much greater then that of sound. The Ultra*LIGHT* imaging system is based on photonics technology utilizing fibre optics, instead of conventional electronics used in ultrasound. The fibre optics allow optical gating of the reflected light waves, which in turn allow depth discrimination of the reflections, similar to the "A-scan" mode of ultrasound. By sweeping the distal end of the fibre optics, a "B-scan" image can be obtained at frame rates close to real-time video.

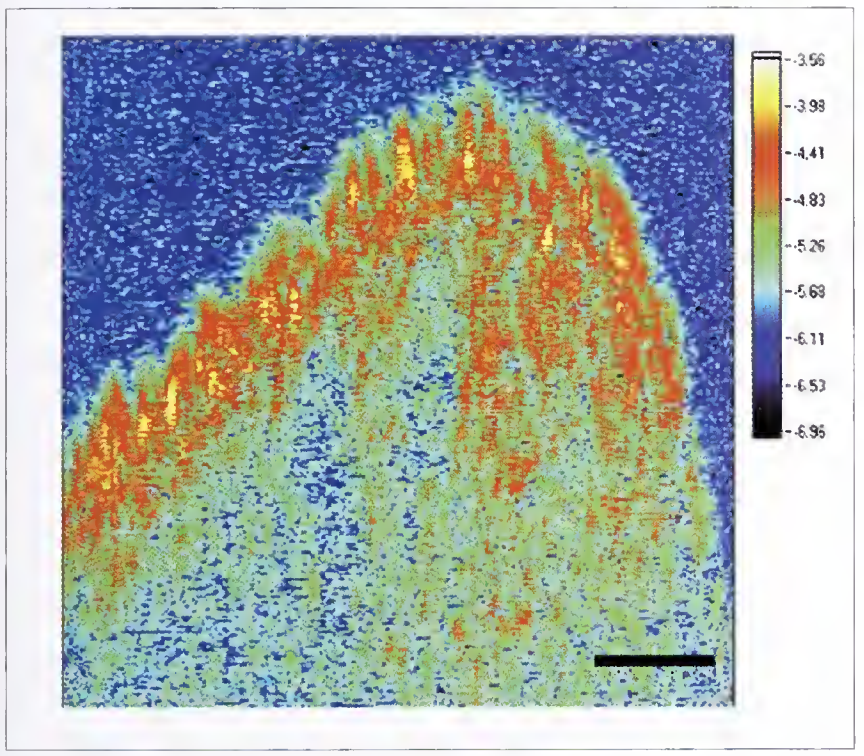

Figure 4. *Bovine gastric mucosa imaged using OCT. Notice the glandular structures. Color bar indicates reflectivity.*

Applications in Gastroenterology

The best techniques currently in use for visualization of the gastrointestinal (GI) tract include endoscopic ultrasonography (EUS) and video endoscopy. The resolution of high-frequency EUS (~70-100 um) is insufficient for the identification of many conditions that perturb tissue microstructure, most notably subtle pathologic changes arising within the superficial layers of the GI tract, in the mucosa and submucosa. Tissue biopsy and histology thus remain the standard of care for detecting microscopic diseases involving the GI tract. Appropriate probes of the Ultra*LIGHT* system can be integrated into GI video endoscopy and offer real-time 2-millimeter deep cross-sectional images of the GI mucosa (see Figure 4). This limited imaging depth is nevertheless sufficient to detect mucosally-based diseases as well as neoplastic invasion into the underlying submucosa, which is of critical importance for prognostic and therapeutic purposes. Pre-neoplastic conditions such as Barrett's esophagus, chronic ulcerative colitis, early flat adenomas, or foci of aberrant colonic crypts would lend themselves very well to this new imaging modality. Currently, detection and surveillance of neoplastic progression within these conditions are suboptimal due to their microscopic nature.

Applications in Respirology

Similar to the GI endoscopy, appropriate probes can also be integrated into video or fibre optic bronchoscopes, allowing cross-sectional imaging of the epithelial layer of the bronchi. Ultrasound cannot be used in the airways due to the need for coupling gel. Currently, there are no alternative imaging modalities providing such information. The use of an Ultra*LIGHT* probe may provide valuable information in terms of biopsy guidance.

Applications in Neurosurgery

The Doppler mode of the Ultra*LIGHT* system may be of particular usefulness in neurosurgery.[9,12] The ability to visualize undersurface small blood vessels is central in avoiding hemorrhage, and in the case of resection, is beneficial in assessing cessation of bleeding. Certain operations targeting the vasculature of the brain might especially benefit from this new imaging modality. Finally, while functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are used to plan surgery by localizing functionally eloquent cortex, an intraoperative method might be beneficial. The Doppler Ultra*LIGHT* can be used in intraoperative imaging studies of microscopic localization of perfusion changes due to stimulation.[13] Such information may complement the pre-op macroscopic functional imaging studies performed using fMRI or PET.

Applications in Pathology

Practically speaking, the Ultra*LIGHT* image resolution would correspond to observing an unstained histology slide under a 100x (total) microscope. Dysplastic (cellular neoplastic alterations) or neoplastic violation of important structures such as the lamina propria or muscularis mucosa might be discernible. This imaging modality would have many unique advantages. First, it would allow in-situ diagnosis of diverse microscopic mucosal pathologies and lesion staging, if relevant. In essence, this "optical biopsy" technique would replace or, at the very least, guide the standard biopsy and histology method. This translates into reducing unnecessary biopsy samples and tissue processing, decreasing patient risk, increasing sampling rate and diagnostic yield, giving immediate diagnostic feedback to physician and patient, and targeting biopsies. Second, the Ultra*LIGHT* may serve as a functional imaging system permitting monitoring of non-neoplastic tissue alterations over time. The natural history of many mucosal diseases at the microscopic level can also be assessed in a minimally invasive manner. The ability to monitor structural cellular changes that are occurring in vivo with time may provide important physiologic information on cell function (and insight into its pathologic transformation) as never obtained before. Third, this imaging modality may permit monitoring of tissue post therapy. Microscopic evaluation *in vivo* of surgical margins during post-therapeutic surveillance of cancer resection or assessment of the adequacy[4,7,8] of photodynamic therapy of neoplastic and preneoplastic conditions are only two examples. Although it is not likely to completely replace biopsy and histology, it may

generally bring under one tent the practice of [illegible] and the practice of pathology. As such, it may initiate a specialty in the field of medicine, that of the [illegible]ic pathologist."

Applications in Other Specialties

Neoplastic diseases of the skin are readily accessible for the Ultra*LIGHT* system.[11] Depth resolved imaging of basal cell carcinoma, squamous cell carcinoma, and other cutaneous lesions might be performed non-invasively to allow determination of the lesion margins. Since an optical based imaging system does not require coupling gel, it also lends itself to the monitoring of wound healing in burn patients. Finally, catheter based probes have been demonstrated to perform subsurface imaging of the walls of blood vessels in both the coronary artery and the microstructure of atherosclerotic plaque.

Conclusion and Future Directions

The Ultra*LIGHT* system is currently being developed at the Ontario Cancer Institute and Photonics Research Ontario, in collaboration with St. Michael's Hospital and Sunnybrook and Women's Health Science Center. Although there have been a handful of other research groups pioneering the optical coherence tomography technology in the world, little previous work has been attempted in Canada, mainly due to the cost involved in developing such technology. At the present time, one of the important tasks of the development team is to design the Ultra*LIGHT* system to be a modular platform which accepts the various above mentioned probes relevant to different applications in order to reduce total system cost.

Finally, optical tomographic imaging systems have some distinct advantages and disadvantages. The shorter wavelength of light greatly improves the image resolution, while the scattering of the light waves within biological tissue greatly limits the imaging depth. Thus, it is conceivable that imaging modalities, such as the Ultra*LIGHT*, will not replace existing imaging systems, but instead, complement conventional medical imaging devices. Because of the cost and complexity involved in such systems, it is unlikely to be employed in general medical practice. Therefore, acceptance by various relevant medical specialties and sub specialties will be a key factor for introducing this imaging modality into practice.

References

1. Izatt J, Kulkarni M, Yazdanfar S. (1997) In vivo bidirectional color Doppler flow imaging of picoliter blood volumes using optical coherence tomography. *Optical Express* 22(18):1439-41.
2. Kehlet Barton J, Izatt JA, Kulkarni MD, Yazdanfar S, Welch AJ. (1999) Three dimensional reconstruction of blood vessels from in vivo color Doppler optical coherence tomography images. *Dermatology* 198(4):355-61.
3. Leeuwen T, Kulkarni M, Yazdanfar, Rollins A, Izatt J. (1999) High-flow-velocity and shear rate imaging by use of color Doppler optical coherence tomography. *Optics Letters* 24(22):1584-86.
4. Barton J, Welsh A, Izatt J. (1998) Investigating pulsed dye laser-blood vessel interaction with color Doppler optical coherence tomography. *Optics Express* 3(6):251-256.
5. Kulkarni M, van Leeuwen T, Yazdanfar S, Izatt J. (1998) Velocity-estimation accuracy and frame-rate limitations in color Doppler optical coherence tomography. *Optics Letters* 23(13):1057-59.
6. Yazdanfar S, Kulkarni M, Izatt J. (1997) High resolution imaging of in vivo cardiac dynamics using color Doppler optical coherence tomography. *Optical Express* 1(13):424-31.
7. Chen Z, Milner T, Srinivas S, *et al.* (1997) Noninvasive imaging of in vivo blood flow velocity using optical Doppler tomography. *Optics Letters* 22(14):1-3.
8. Chen Z, Milner T, Wang X, *et al.* (1998) Optical Doppler tomography: Imaging in vivo blood flow dynamics following pharmacological intervention and photodynamic therapy. *Photochem & Photobiol* 67:1-8.
9. Okumura A, Takenaka K, Nishimura Y *et al.* (1999) Intra-operative optical method using intrinsic signals for localization of sensorimotor area in patients with brain tumor. *Neurol Res* 21(6):545-52.
10. Erbel R, Ge J, Gorge G, *et al.* (1998) New imaging methods for visualizing coronary arteries. *Z Kardiol* 87 Suppl 2:61-73.
11. Happe M, Freitag M, Stucker M *et al.* (1997) High resolution 20 MHz ultrasound diagnosis in dermatology for noninvasive imaging of malignant melanomas. *Z. Arztl Fortbild Qualitatssich* 91(4):347-53.
12. Machens HG, Mailaender P, Rieck B, Berger A. (1994) Techniques of postoperative blood flow monitoring after free tissue transfer: an overview. *Microsurgery* 15(11):778-86.
13. Malonek D, Dirnagl U, Lindauer U, *et al.* (1997) Vascular imprints of neuronal activity: Relationships between the dynamics of cortical blood flow, oxygenation, and volume changes following sensory stimulation. *Proc Natl Acad Sci USA* 94:14826-31.

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The University of Toronto as a World Leader in Medical Genetics: Past, Present and Future

Charis Kepron, M.Sc. (0T4), Chris Lane, M.Sc. (0T4), David Maslove, B.Sc. (0T4), Vladislav Miropolsky, B.Sc. (0T3), and Peter Zakrzewski, B.Sc. (0T4)

Over the last 50 years, the use of genetics in medicine has undergone a vast transformation. While formerly having a very limited clinical application, such as the diagnosis and assessment of rare disorders, it has since blossomed into a field of research full of great promise. The University of Toronto has played a number of important roles in this transformation, including work in Muscular Dystrophy, Cystic Fibrosis, Alzheimer's Disease, genetics of the human immune system, and most recently, mapping chromosome 7 as part of the Human Genome project.

Duchenne Muscular Dystrophy (DMD) is the most common and devastating of the muscular dystrophies, affecting 1 in 3500 male newborns. It is a lethal X-linked genetic disease, and affected individuals will usually present with muscle weakness around age 3, lose the ability to walk by age 13, and do not usually survive beyond their early 20's, dying as a result of respiratory or cardiac failure.

For decades, this disease frustrated researchers and clinicians until 1983 when the DMD gene was mapped to a specific region on the short arm of the X chromosome. This significant breakthrough became the starting block in a race to identify and clone the DMD gene. The two established front-runners in this race were a research group at Harvard University Medical School and a group at the Hospital for Sick Children in Toronto headed by Dr. Ronald Worton. Throughout the mid-1980s, the two groups kept pace and both were able to successfully clone various segments of DNA from the X chromosome where the DMD gene is located. In 1987, both groups crossed the finish line. Both the Toronto and Harvard lab reported cloning the complete DMD complementary DNA (representing the complete DMD gene transcript) in parallel, but by using different molecular techniques.[1,2] Unfortunately for the Toronto group, the team from Boston seems to have been given popular credit for having "discovered" the DMD gene even though both groups produced the same results at almost the same time.

The Boston group went on to isolate and characterize the gene product, a protein known as dystrophin. The Toronto team is credited with much of the subsequent DMD gene mutational analysis which established that over 70% of DMD cases are due to either deletions within the gene or complete or partial duplications of the gene.[3] In turn, this information paved the way for the development of methods used in prenatal diagnosis as well as methods to identify potential carriers of the disease.

The University of Toronto also played a critical role in generating the knowledge currently fuelling Cystic Fibrosis (CF) research. Clinical research examining family histories for CF first appeared in 1946 and indicated that the disorder was genetic in nature and probably due to a single recessive gene.

In the early 1980's, a major biochemical defect in patients affected with CF was uncovered. The discovery that organs affected by CF have epithelial tissue impermeable to chloride ions led to the measurement of chloride ion concentration in perspiration, a procedure that became the new cornerstone for diagnosing CF. As the studies of chloride ion impermeability progressed, many research groups engaged in a quest to find the gene responsible for this phenomenon. In 1989, a collaborative effort led by Drs. Lap-Chee Tsui and John Riordan at the Hospital for Sick Children and by Dr. Francis Collins at the Howard Hughes Medical Institute at the University of Michigan announced that the target gene had been isolated. The protein product from this gene was named Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) because of its role in chloride ion transport.[4]

While identifying the gene, the team also found an abnormality that resulted in the loss of a single phenylalanine residue that accounted for up to 70% of all CF cases. Toronto's leading role in this discovery has resulted in multiple studies and the identification of many other mutations of the gene.[4] Toronto researchers have also identified how CFTR interacts in the cell to transport chloride ions and they have suggested several options for treating Cystic Fibrosis.

Since these discoveries of the 1980's, genetic research in Toronto has continued to be prolific. Recent work in the field of Alzheimer's Disease has helped to solidify the University of

reputation as a major international force in medical research. Alzheimer's Disease is a neurodegenerative disorder characterized by progressive memory and cognition loss. It is accompanied by physical changes in the brain such as loss of neurons, deposits of extracellular amyloid plaques and "tangles" (tangles between neurons. Epidemiological and molecular genetic data suggests that although there are likely multiple factors influencing the cause of Alzheimer's, genetic factors play a prominent role.

At the University of Toronto's Centre for Research in Neurodegenerative Diseases, Dr. Peter St. George-Hyslop, Director of the Centre, and his team have received international acclaim for their work in the genetics of neurological diseases. In 1995, they identified and cloned two defective genes known as presenilin 1 and 2 that accounted for familial early-onset Alzheimer's Disease.[5] Linkage analysis mapped the loci for the two genes to chromosomes 14 and 1, respectively. Mutations in the presenilins cause Alzheimer's Disease by inducing abnormal processing of the ß-amyloid precursor protein and the accumulation of a toxic derivative, amyloid-peptide, in patient's brains.

According to a study published in September 7, 2000 issue of Nature magazine, Dr. St. George-Hyslop's research group has found a completely unknown protein, nicastrin, that regulates presenilin-mediated production of the amyloid ß-peptide.[6] More importantly, they discovered a way to manipulate nicastrin to regulate the production of the harmful amyloid ß-peptide. This research could ultimately lead to new drug treatments that could significantly improve the lives of Alzheimer's patients.

In addition to cloning genes responsible for specific diseases, researchers at University of Toronto have also played an integral role in cloning genes of crucial importance to the body's immune system. In 1984, a group led by Dr. Tak Mak at the Ontario Cancer Institute succeeded in cloning and sequencing the genes coding for the ß-chain of the T-cell receptor molecule.[7] Dr. Mak's group was able to isolate and clone mRNA from a human leukaemic T-cell line, and then to exploit key differences between B- and T-cells in order to determine which clones coded for the T-cell receptor. The determined sequence predicted a protein structure very similar to that of the immunoglobulins produced by B-cells.[7]

The impact of Dr. Mak's genetic breakthrough has been far-reaching. As research in the biomedical sciences expands, researchers are becoming increasingly aware of the importance of the immune system in the etiology and pathogenesis of many diseases, both infectious and otherwise. T-cells mediate many immune processes, relying on the incredible diversity of their receptors to recognize infected cells. Advances in our understanding of T-cell receptor biology will likely impact on our understanding and treatment of innumerable conditions including cancer, autoimmune disorders and heart disease.

The field of medical genetics has evolved beyond simply isolating and sequencing genes responsible for specific diseases. Today, most of the attention in the field of medical genetics is focused on the Human Genome Project, a joint international effort aimed at sequencing each of the approximately 30,000 human genes. Conceived in the mid-1980's, and formally started in 1990, the Human Genome Project has gone from virtual anonymity to celebrity status, often reaching the front pages of major international newspapers. Many scientists expect the findings from the project to revolutionize the diagnosis and treatment of genetic disorders, and eventually aid in unravelling the genetic components of common and complex disorders such as heart disease and cancer.

Dr. Lap-Chee Tsui, Head Geneticist at the Hospital for Sick Children, and his research group, leads Toronto's contribution to the Human Genome Project. They are attempting to construct a physical, genetic and transcription map of the "long arm" region (7q) of chromosome 7, which has been estimated to account for 5% of the human genome. Diseases potentially associated with abnormalities of chromosome 7 include cancers of the breast, ovaries, prostate and pancreas.[8]

Constructing a physical map of the chromosomes is an important stepping stone in genomic research, and Toronto's contribution on chromosome 7 is an essential part. The mapping data provided by the project will give scientists an invaluable tool in their quest to elucidate the regulatory mechanisms of gene expression in human biology.

Although the field of medical genetics has fostered many important discoveries in the past, we are only now beginning to realize its potential for changing both the research and clinical face of medicine, and ultimately changing the overall delivery of health care in society. As Dr. Lap-Chee Tsui contends, "Genomics is more than just sequencing. It is also understanding the function of genes, not just scientifically, but also [the] implications for society in the post-genomic era.

References

1. Burghes, A.H.M., Logan, C., Hu, X., Belfall, B., Worton, R.G. & Ray, P.N. (1987). A cDNA clone from the Duchenne-Becker muscular dystrophy gene. *Nature.* 328:434-437.
2. Koenig, M., Hoffman, E.P., Bertelson, C.J., Monaco, A.P., Freener, C. & Kunkel, L.M. (1987). Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. *Cell.* 50:509-17.
3. Prior, T.W. (1991). Genetic analysis of the Duchenne muscular dystrophy gene. *Arch. Pathol. Lab Med.* 115:984-990.
4. Welsh, M.J. & Smith, A.E. Cystic Fibrosis: The genetic defects underlying this lethal disease have now been shown to eliminate or hobble a critical channel through which a constituent of salt enters and leaves cells. *Scientific American.* December 1995.
5. Sherrington, R. et al. (1995). Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature.* 375: 754-760.
6. Yu, G. et al. (2000). Nicastrin modulates presenilin-mediated notch/glp-1 signal transduction and BAPP processing. *Nature.* 407: 48-54.
7. Yanagi, Y., Yoshikai, Y., Leggett, K., Clark, S.P., Aleksander, I. & Mak, T.W. (1984). A human T cell-specific cDNA clone encodes a protein having extensive homology to immunoglobulin chains. *Nature.* 308: 31-33.
8. Chromosome 7 Research Website: http://www.genet.sickkids.on.ca.

Medical Education below the 49th Parallel

Chris McIntosh, M.Sc. (0T1)

Time to Heal: American Medical Education from the Turn of the Century to the Era of Managed Care

Kenneth M. Ludmerer

Oxford University Press
1999, 514 pp
Hardcover, $56.00

Kenneth Ludmerer, an internist and medical historian from Washington University, has put a mammoth effort into producing this book, a history of American medical education in the twentieth century. One hundred pages of endnotes detail his exhaustive search through university and hospital archives to glean the material for this hefty volume. The result? An impressive work that skilfully describes the evolution of the American medical school from the low-quality turn-of-the-century proprietary schools to the medical powerhouse that dominated most of this century. At the same time, the book asks us to ponder what the system will look like after the managed-care revolution. Without a doubt, this book should be read by anyone contemplating obtaining any part of his or her medical education in the United States.

The book is divided into three sections. The first – Fulfilling the Social Contract: Medical Education as a Public Trust – describes the sorry state of the American medical school at the turn of the century. Most schools at this time were proprietary, that is, instructor-owned commercial ventures with tiny faculties, exorbitant fees, and poor quality instruction. This changed when a searing critique was published by one Abraham Flexner. The Flexner report, as it became known, resulted in a revolution that transformed the system from one of the worst in the world to one unsurpassed anywhere.

The key to this revolution was in establishing medical education as a public trust. Recognising that it was in the public interest to have well-trained doctors, the government not only passed laws that created high standards but also provided funds to ensure that the standards could be met. This concept of the public trust is the overarching theme of *Time to Heal*. As the book progresses through the second and third sections, dealing with the expansion of medical schools in the resource-abundant 1950s and 1960s and the subsequent challenges of the greedy 1980s and cost-conscious 1990s, the slow erosion of that trust becomes clear.

Another theme in the book is the struggle to keep education as an equal partner in the medical school's tripartite mission of education, research and patient care. The squeeze came first from research during the massive post-World War II expansion of biomedical research. Since then, the era of cost-containment and health maintenance organizations (HMOs) has resulted in both education and research being eclipsed by patient care, as institutions try to stay afloat financially by pushing many patients through the system as quickly as possible. The idea that a medical school is first and foremost a place to teach medical students has been under attack almost since its inception.

The title of the book, *Time to Heal*, can be taken several ways. The most obvious reading is suggested by the tone of Ludmerer's final two chapters on the evils of managed care, that it is time to heal the system before things get any worse. But the title also suggests that what has been lost in the current system is the time to learn to heal. As the changing nature of medical practice shifts the educational focus from inpatient to outpatient care, and as HMOs force a higher 'throughput', students and residents are losing the time to ponder and reflect, and are increasingly becoming just another cog in the patient processing profit-turning machine.

Canadians reading this book could hardly be blamed for feeling smug. We shouldn't. Our country has an even greater sense of our health care system as a public interest, and we have much more to lose if we abuse the public trust.

There is much more in this book for Canadians than ominous warnings, however. The chapters describing how undergraduate and graduate medical education programs came to be structured the way they are (clerks, interns, residents) are fascinating. The struggle by American women and minorities to gain an equal footing in medical schools parallels similar events in Canada. There are very few direct Canadian references, but McMaster does get a brief mention for introducing problem-based learning.

If *Time to Heal* suffers from one big flaw, it is that the middle of the book is terribly dull. History books need heroes and villains to keep the reader awake. In between the heroic Abraham Flexner and his reforming compatriots in the first section and the villainous insurance companies and HMOs in the last third, there isn't much to hold one's interest. Still, Ludmerer the historian deserves credit for putting accuracy and balance ahead of flash and style, even if Ludmerer the storyteller suffers a bit from the effort.

I would recommend this book to anyone who has an interest in medical history, and it is surely required reading for anyone contemplating a move to the United States, either for education or practice.

Chris McIntosh is a fourth-year clerk who reviewed this book while experiencing the American medical education system first-hand, on an elective in San Francisco.

Modernizing a Classic Curriculum

Elana Lavine (0T2)

The Johns Hopkins University School of Medicine Curriculum for the Twenty-First Century

Catherine D. DeAngelis, Ed.

The Johns Hopkins University Press, 1999, 248 pp
Cost: Paperback, $33.50

While reading this recently published history and description of the current Johns Hopkins medical curriculum on the subway, I was approached by a talkative graduate of that very program. "I noticed you reading that particular book," this person explained, "and was quite curious. We had all heard about its publication, but I don't think I've ever seen a fellow student actually read it."

Unfortunately, I can understand why this slim volume might not reach the shelves or knapsacks of many medical students. This publication is a series of essays written by various Hopkins faculty members and deans, all of whom played important roles in the development of a "Curriculum for the Twenty-First Century".

Johns Hopkins led the way in developing the North American medical school model. In the late 19th century, most medical schools were proprietary, meaning they were owned by their faculty and had only nominal roles in their associated universities. Their facilities were poor, the length and quality of training highly variable, and their graduates often learned how to care for patients only after starting their own practices.

The Hopkins model was new. It was four years long – a student spent the first two in basic sciences and two more in the clinical specialties. Sound familiar? The model also included a revolutionary admission requirement – a college degree. Instructors were actively engaged in research in their own fields. Finally, a strong relationship between the university and the medical school was developed and cultivated.

But as the 20th century passed by, other schools gradually modified the Hopkins model. The McMaster model of independent study and small groups began to be adopted, in whole or in part, by many of North America's leading medical schools. In 1987, a report was circulated at Hopkins that listed several goals, including the reduction of lecture hours, the introduction of free afternoons into weekly scheduling, a four-year longitudinal course in clinical medicine, and weekly sessions for the discussion of current published research and its implications. So began the process of achieving these goals, championed by Catherine De Angelis, then the associate dean for academic affairs (and editor of this book).

The book is a plain, scientific-paper style text, with black and white figures and tables inserted into the body of each chapter. References and bibliographies are generous. Each chapter covers a different element of the curriculum, including the basic science components of Years 1 and 2, the Bridging Sciences of Year 2, and the Clinical Clerkship. Chapters are also devoted to the development of information technology and computer resources for curriculum support, and to the evaluation of the curriculum

Even for a reader with an interest in medical education, it is hard to digest paragraphs that explain committee infrastructure and administrative issues. For the strong-willed, the ability to skim the more administrative section of the text does bear fruit, as some sections are quite interesting. Hopkins' students benefit from a course called Physician and Society, which includes content on ethical theory, history of medicine, cultural anthropology, health economics, and even societal perceptions of health and illness as depicted in the arts.

Another novel idea is the Introduction to Clinical Medicine course, among whose goals are to "expose students to real-world community experiences" and "provide a context for understanding social and cultural factors in health and illness from a community perspective." In short, this course involves spending scheduled time with a handpicked community physician. It is entirely separate from the course offered in Clinical Skills. Rather than learning how to percuss or palpate, the student is supposed to develop rapport with patients and gain an acculturation to the world of the MD.

This small, dense book does allow a curious medical student to draw comparisons between their own hometown curriculum and the Johns Hopkins approach. The increasing presence of small group learning in Canadian medical curricula, as well as the growing emphasis on the assimilation of novel research into the lecture venue, are similarities which come to mind. However, the lecture format has not been entirely stricken from the Hopkins curriculum, which is more similar to the University of Toronto's than McMaster's.

The book is a brief, interesting tale of how one school has tried to incorporate new trends into its original philosophy of medical education. Unfortunately, it also contains overwhelming amounts of administrative, numerical, and infrastructure information. With some effort, however, the reader can extract interesting concepts and approaches to medical education, and learn a little bit more about learning.

Elana Lavine held the University of Toronto Medical Society position of Vice-President, Curriculum from 1998-2000.

A Monster Psychiatrist on the Loose in Toronto

Christopher Tam, B.A. (0T2)

Headhunter

Timothy Findley

Harper Collins Canada
2000 (first published in 1993)
512 pp
Paperback, $18.95

"And this also," said Marlow suddenly, "has been one of the dark places of the earth."

Joseph Conrad's
Heart of Darkness

The air is amber and fetid. Sturnusemia, a new plague, is taking hold. The rich and privileged are locked in a power struggle. Children are being mysteriously rendered catatonic.

This 'dark place' is not one of the river stations that Conrad's Marlow encounters on his journey up the Congo but a futuristic Toronto – the setting for Canadian author Timothy Findley's ambitious 1993 novel, *Headhunter*.

The story begins with a burst of originality: Lilah Kemp, a bibliophile with schizophrenia, accidentally allows Kurtz to escape from page 92 of *Heart of Darkness*. The reader is tempted to dismiss this event as an acute exacerbation of Lilah's illness, but Findley soon makes it clear that Kurtz is all too real. Indeed, T. Rupert Kurtz, MD, FRCP(C), is the Director and Psychiatrist-in-Chief of the Parkin Institute of Psychiatric Research in Toronto.

Image source: Robert Resing

Like his counterpart in Conrad's Africa, Kurtz – the headhunter – has a God complex and wields his absolute power unethically. Patients are not individuals who need help but financial donors who can be persuaded to support the Institute's activities. Simply put, Kurtz is a monster. He steals patients from colleagues, breaks patient confidentiality, remains silent over a pedophile's activities and commits the sane against their wishes.

Powerless to reduce Kurtz's domination, Lilah enlists the help of Charles Marlow, a neighbour, who coincidentally works as a staff psychiatrist at the Parkin Institute. It is he, Lilah believes, who must ultimately confront Kurtz and bring him to justice.

Literature lovers will delight in the homage Findley pays to classic novels. Characters are drawn not only from Heart of Darkness but also from The Great Gatsby and Madame Bovary. Findley marvellously weaves together the actions and fates of the lonely tycoon James Gatz and the bored doctor's wife Emma Berry. *Headhunter* also contains allusions to Wuthering Heights, Frankenstein, and Moby Dick, among others.

Like many successful novels, *Headhunter* manages to combine seriousness and satire. From the comedic standpoint, it is fortunate for the Canadian reader that Findley has set his story in Toronto. Readers will chuckle as Findley pokes fun at Rosedale's elite or the University of Toronto's Robarts Library, a building that had "passed as architecture when the whole world sucked its thumb."

One aspect of this novel that may not appeal to readers is its sheer size. *Headhunter* is a daunting narrative filled with a myriad of characters and subplots. While each of these subplots is in some way connected to the main plot, the hurried reader may be tempted to read only those parts involving Kurtz and Marlow. Moreover, if the book is left unread for a few weeks, the reader risks forgetting much of the story line.

Like Findley's earlier works, *Headhunter* is critical of authority and the ways that institutions exert influence in both the public and private spheres. For Findley, a hero must challenge the lies and oppressive regimes that others have passively accepted as status quo. *The Wars* (1977) is anti-military, *Famous Last Words* (1981) is anti-fascist, and *Not Wanted on the Voyage* (1986) is anti-organized religion. Is *Headhunter* supposed to be anti-psychiatry?

In his preface, Findley claims that this novel is about what could happen if the wrong people were to be entrusted with the care of the mentally ill. But by concluding with the ironic words that Headhunter is "only a book…Just a story," Findley obviously doesn't want us to become too comfortable with psychiatry as practised today.

In one of the most memorable passages in the novel, one of the characters, well-read Nicholas Fagan, summarizes the function of literature:

These characters drawn on the page by the makers of literature are distillations of our thwarted selves. We are their echoes and their shadows. They move through our muddied lives at a clarified pace. What we cannot describe, they articulate. What we cannot imagine, they reveal. What we cannot endure, they survive.

As the reader of *Headhunter* discovers, characters originally thought to exist only in literature can also inhabit the real world. Findley successfully blurs the line between fiction and reality. Readers will finish this ingeniously crafted novel with a sense that something has been jolted out of place. They too may wonder whether any of the characters or events portrayed in Findley's *Headhunter* has already been unleashed into the world.

An Updated Respiratory Classic

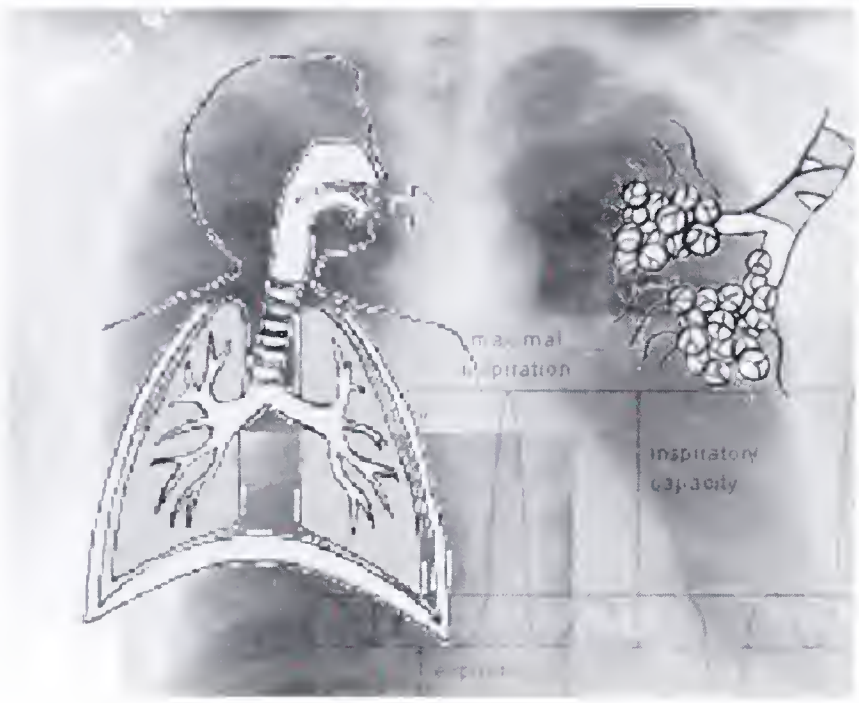
Amy S M Tam, B.Sc (0T2)

Respiratory Physiology: The Essentials, 6th edition

John B West

Lippincott Williams and Wilkins
1999, 171 pp
Paperback, $48.50

One of the challenges of undergraduate medicine is the understanding of pulmonary physiology. With its many unique biological and physical properties, the lung can be a demanding subject, regardless of a student's level of training. The success of *Respiratory Physiology*, now in its 6th edition, rests largely on John West's appreciation of that fact. So fundamental and broad based are its topics that West's book is useful to any level of student, from first year undergraduate medicine to postgraduate training. First published in 1974, it has been translated into thirteen languages, and is one of hundreds of publications by the author.



West is a highly accomplished researcher and has held numerous academic posts, including principle investigator for NASA Spacelabs. He is also an adventurer, serving as physiologist for one of Sir Edmund Hillary's Himalayan climbs.

Each topic in *Respiratory Physiology*, from lung structure and function to pulmonary function testing, is handled in an organized and concise manner. Subjects made complex and confusing in the hands of lesser teachers are presented in straightforward discussions with the aid of simple analogies and line diagrams. For example, West compares the diffusion properties of different gases to the rate sheep can enter a field through varying sizes of gates. To build interest, each chapter finishes with a problem that ties in with future chapters. None of the topics or illustrations is superfluous. Appendices with equations, problems, and references seem to be standard elements in introductory pulmonary physiology texts, and this book is not an exception. Overall, *Respiratory Physiology* is versatile enough that undergraduates can read it cover-to cover quickly to gain a broad understanding of the lung; more advanced readers can use the sections independently as refreshers or springboards to more the detailed discussions listed in the appendices.

On the downside, the text has all of the disadvantages of summary-style books. The physical size of the book limits the space available for diagrams, and some of the electron micrographs are poorly reproduced. Topics are not explored in depth. Readers should be well versed with basics of fluid flow and diffusion to gain maximal benefit from the text because these topics are introduced relatively late. While principles such as Fick's law of diffusion are outlined in Appendix A in equation format, this may be a difficult jump for students with pure biology or non-science backgrounds. As well, some complicated concepts that are usually derived from basic principles in larger volumes are presented in a matter-of-fact narrative style. This writing style and Dr. West's opinions can detract from the reader's excitement of "discovering" new concepts by following more descriptive and detailed discussions.

Respiratory Physiology is on par with similarly priced books written about pulmonary physiology. Its shortcomings mean that it is ideal only for certain students – those with a background in physiology or biophysics who can get away with owning the most condensed text possible. Students should also know that West has authored several other texts, including *Pulmonary Pathophysiology*, a book that acts as a continuation of *Respiratory Physiology* and focuses on disease states.

The Vanishing Art of Prognosis

Lilia Malkin, B.Sc. (0T1)

Death Foretold: Prophecy and Prognosis in Medical Care

Nicholas A. Christakis

University of Chicago Press
1999, 296pp
Hardcover, $46.50

On my first night on call during my internal medicine clerkship rotation, I admitted a woman in her early 40s to the Internal Medicine service for an apparent pulmonary embolus. 'Linda' was polite, professional, and composed, in spite of her terrifying chest pain accompanied by inability to breathe and a five-day old diagnosis of lung cancer. Her week in hospital brought invasive investigations, medications, an invitation to participate

in a clinical trial, as well as daily visits from a 'bright-eyed and bushy-tailed' clinical clerk. I came bearing my stethoscope, her chart, and updates on the numerous lab and diagnostic imaging studies. At the end of her week with us, Linda received the relatively 'good' news that her lung nodule was not a primary, but a metastatic lesion from her colon cancer. A visit to the oncology clinic followed, where Linda was presented with her treatment options. For the first time in several days, I watched her break down in tears, as the prognostic implications of her new diagnosis were explained by the oncologist with admirable clarity and empathy. Although Linda's prognosis was illustrated only in statistical terms, the explanation of potential outcomes with different therapeutic options (and lack of treatment) made it easier for her to choose how she wanted to spend the remainder of her life.

If you enjoyed reading the preceding clinical vignette, you will welcome Nicholas Christakis' down-to-earth style of discussing one of the most elusive aspects of medical care: prognosis. Christakis combines his experience practising medicine with his sociology background to address the issues surrounding prognosis and its seemingly dwindling role in clinical practice in a readable and thought-provoking text.

As the title implies, Christakis devotes a large portion of his book to discussing the implications of predicting outcome of disease for end-of-life planning and palliative care in terminally ill patients. Nevertheless, he makes numerous salient points that may be generalized to prognosis of even the most benign conditions.

In a compelling introduction, Christakis argues that compassionate prognostication has a key role in improving the quality of patients' life and death. He presents the physician's duty to provide a prognosis as a moral obligation to one's patients and laments its exodus from routine practice. Christakis asserts that as medical science marches ahead, treatment, rather than prognosis dominate the focus of physician-patient communication. He then compares recent and outdated medical textbooks, showing that the amount of discussion allocated to prognosis has been rapidly diminishing over the last century. Unfortunately, according to Christakis, this trend of glossing over the prediction of outcome has not been beneficial to the patient, producing avoidable distress, particularly at the time of death. Christakis rationalizes the physicians' reluctance to predict outcome, attributing it to fear of uncertainty, lack of training at delivering "bad news", as well as concerns with respect to a "self-fulfilling prophecy".

A neurosurgeon told the students in our first-year clinical skills group that he "never [tells] his cancer patients how long they have left to live". His simple reason was that he may be wrong – people had outlived his expectations on numerous occasions. Perhaps it is kinder not to limit someone's life expectancy, but rather leave them with their own hopes?

Christakis contends that a grim prognosis does not imply that hope must be extinguished. However, he also discusses the dangers of biased and overly optimistic predictions that can result in unwelcome therapeutic interventions and inappropriate heroic measures at the time of death. In this era of judicious resource allocation, Christakis dangles the carrot of reduced health care costs as justification for increasing the importance of prognosis. Finally, in addition to stressing the physician's duty to prognosticate, Christakis also provides strategies to do so in a compassionate and effective manner.

Death Foretold does have a few minor weaknesses. Christakis has a tendency to rephrase ideas in a manner that soon becomes redundant. Another limitation, albeit one acknowledged by the author, is that he draws a considerable amount of information presented in the book from the experiences of internists – a specialty known for treating chronic conditions, rather than acute injury or disease. Would the picture be different if more physicians from other specialists were consulted?

That said, this book is well written and easy to read. The research is thorough as well. Christakis supplements his own qualitative and quantitative research findings with the work of experts in many fields, including the social sciences, bioethics, and palliative care. The references are extensive and contain many publications that an interested reader may choose to explore. Christakis has also added numerous endnotes that contain expanded references, discussions, and explanations for studies and arguments presented in the body of the text. This is particularly convenient, as it allows the reader to refer to the in-depth material at leisure, without feeling overwhelmed by minor details.

In summary, *Death Foretold* is a valuable resource to MDs and MDs-to-be alike, and not only because Christakis does a wonderful job describing the value of prognosis as both a science and an art of medical practice. This book pushes its readers to rethink the way they want to practice medicine, and that is what makes it worth reading.

Is There More to Life than Medicine?

Jacqueline H. Perry, B.Sc (OT1)

Doctors Afield

Mary G. McCrea Curnen,
Howard Spiro,
Deborah St. James, Eds.

Yale University Press
1999, 264 pp
Hardcover, $42.50

As the editors state in the preface to *Doctors Afield*, their "intent was to provide a book that would let the everyday practitioner understand that he or she had stories to tell, roads to walk, pictures to paint, tunes to play – and that there is life outside, even after, medicine." Mission accomplished. Although the path the editors took did have some shortcomings, the overall journey leaves the reader in a revelation of self-discovery, with the courage to pursue their avocations at a higher level. This book demonstrates that 'ordinary' physicians like us often achieve extraordinary things.

Doctors Afield is a compilation of twenty-seven vignettes, twenty-three of which describe living individuals, including twenty-one men. When soliciting these narratives, the editors applied two simple criteria: First, the individual must have attended medical school. Second, the individual must have won some repute outside medicine. The contributors were asked to write a brief essay describing what they had obtained from their dual careers and how these second careers had helped their practice of medicine and their patients. Originally, the editors personally contacted physicians around New Haven, but eventually they broadened their scope. Even so, the book regrettably describes only the lives of American physicians.

Image source: NASA

The book's title is taken from a column that appeared in the *New England Journal of Medicine* from 1952-69 which focused on physicians who were doing unusual things. For the book's purposes, the categories in which a doctor may have been deemed to be 'afield' include the visual arts, music, literature, fun and games, government and university, astronauties, the spiritual life, and collecting. Remarkably, a few of the contributors overlap more than two of the categories.

The most famous physicians in the book are probably Gertrude Stein, William Thornton, and Carlo Levi, and even they are not first-tier celebrities. Rather than choosing to highlight fame, the editors strove to "document the accounts of humbler writers and artists, whose successes seemed achievable...." The only problem with this approach is that many of the much-touted accomplishments seem almost too easily achieved! While reading *Doctors Afield*, I felt that many of my classmates could have easily authored a section. Then again, in the current atmosphere where 'well-roundedness' is the backbone of a medical school application, it is possibly becoming more commonplace to tackle hobbies with as much zeal as a career. Nevertheless, the effort to move 'afield' should not be underestimated, as it is a tremendous task of balance and commitment. *Doctors Afield* is a reminder that all physicians who take on 'extra lives' should be recognized, appreciated, rewarded, and respected. Yet, our acknowledgement of such physicians usually falls short.

The twenty-seven narratives richly describe the joy these physicians receive by pursuing other endeavours and how these extramural pursuits and their medical practice nourish each other. One complaint is that the authors too often focus on the 'why' rather than the 'how'. Readers desiring to embark on such a journey might have benefited from time-management advice.

As *Doctors Afield* has twenty-seven different authors, the reality is that some vignettes are intriguing and compelling, while others can be skipped with little loss. Writing styles vary, for better or for worse. In the end, though, *Doctors Afield* is a truly inspiring book that ignites the soul's craving for other opportunities. It is a pleasant, easy read for anyone in the medical profession. A final note from Daniel Callahan of The Hastings Center: "In sports, they call it cross-training; in medicine it can rightly be called cross-enriching: putting together a life of medicine and another pursuit – music, art, politics, or poetry. The sketches in this book are themselves enriching, showing us the possibilities for living a fuller, more creative life."

During the mayhem of medical school, Jacqueline Perry has managed to venture 'afield' herself and achieve multiple certifications in kayaking and sailing.

Healthy Diet for Dummies

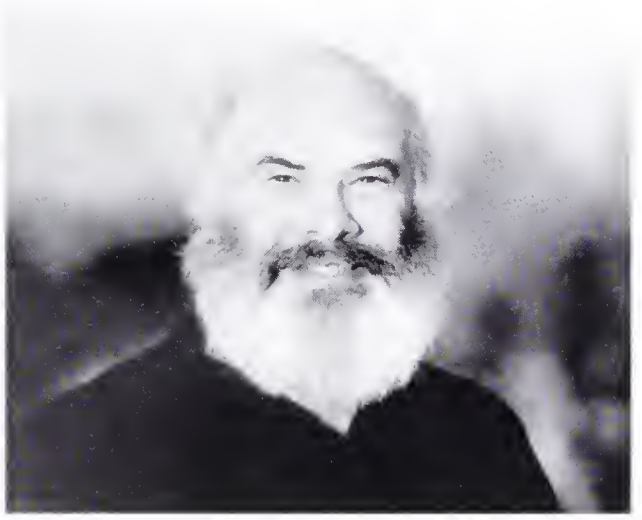
Wilson W. Marhin, Ph.D. (0T3)

Eating Well for Optimum Health: The Essential Guide to Food, Diet, and Nutrition

Andrew Weil

Alfred A. Knopf, 2000, 307 pp
Hardcover, $38

The last three decades have witnessed an explosion in the public's interest in alternative medical therapies and lifestyles, irrevocably altering the nature of the doctor-patient relationship. Physicians are teetering on their god-like pedestals and an increasingly educated public commonly questions physician judgment. Many attribute the cause of this fundamental change to the societal revolutions in the 1960s. Out of this decade rose a desire to challenge previously unassailable authority and drive for personal empowerment in one's life. This movement extended across all facets of North American life, from politics to health. Individuals began to seek 'natural' medicines as a form of renewal, a return to our past when we lived in a less polluted world. These remedies were initially classified as alternative therapies, and people flocked to their promise of a simpler, cleaner lifestyle. Yet this philosophy continued to evolve, developing into complementary medicine in the 1980s, and later a fusion of traditional and alternative medicine called integrative medicine in the late 1990s. This evolution is clearly mirrored in the life and writings of Dr. Andrew Weil.



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Weil, who graduated from Harvard Medical School, is probably the most well known advocate of alternative medicine in North America. His philosophy on the practice of medicine has been aptly summarized by a quote published in USA Today: "He is the USA's leading proponent of integrative medicine, which combines traditional clinical practices with alternative and herbal remedies.... He has hit a medical nerve." Indeed, Weil has hit a nerve, for better or for worse.

Weil's latest book, *Eating Well for Optimum Health*, is billed as the "essential guide to food, diet, and nutrition." Weil sets out to show his numerous followers how to make educated choices about what to eat and how to prepare their meals. He stresses that there are no 'good' or 'bad' foods; everything should be eaten in prescribed amounts based upon your individual nutritional requirements and exercise level.

The chapter on nutrition, which gives a simple yet thorough description of the major macronutrients and micronutrients, is probably unnecessary for a medical student. More practical are the complete weekly menus (with 85 simple recipes) for use in the home and at the restaurant.

Apart from all the talk of calories and bad, high glycemic index, white, fluffy bread, this book also includes thoughtful, sometimes humorous anecdotal accounts from Weil's fans who have embraced his philosophy of life. For example, Weil describes individuals who do not eat and derive their sustenance from the light of the sun. If this is too much information for you to digest, there is also a more believable section containing answers to commonly asked questions.

So what did I think of the book? As one whose mouth waters whenever I walk past a Kentucky Fried Chicken outlet, I approached this book with a great deal of trepidation and greasy fingers. This book, like Weil's life and career is a study in contradictions. In the introduction Weil stresses the concept that there are no 'bad' foods, and any macronutrient can be include in your daily diet if it is eaten in the right proportions. Yet, it is clearly evident throughout the book that Weil is preoccupied with promoting his own predominantly vegetarian lifestyle. Although the book is well written, there are areas that can be quite difficult to understand for readers lacking a basic biochemistry background. For example, the Krebs cycle and ATP are frequently mentioned yet not adequately described.

Weil attacks rapid weight reduction schemes, reserving special criticism for high protein, low carbohydrate regimes such as those proposed in the Atkins and Montignac diets. However, his rejection of these weight-reducing plans is not founded upon rigorous scientific proof but upon what he describes as "common sense." Indeed, he seems to disdain the scientific method in favour of a seemingly more "natural" approach that can be best described as "if it makes you feel good, it must be good for you." Weil's evidence consists of a series of "Healing Stories," testimonials from individuals who have written to Weil extolling the virtues of his teachings.

Overall, I thought that the book was a bit preachy, but that it did convey important information in a relatively simple manner. Weil's dietary suggestions are simple to understand and easy to employ. I also approve of his views concerning weight. He suggests that many "overweight" individuals are overly concerned with the North American concept of emaciated beauty. Weil's advice for these individuals is to accept their body size, and minimize the chance that being slightly obese will shorten their

lives by exercising and committing to a healthy lifestyle.

Despite my criticisms and mild skepticism, after reading this book I discovered that I had become more knowledgeable about my diet. Although I am not claiming to be a convert, I am paying more attention to what and where I eat, as well as how my food is prepared. And if that is the very least that Andrew Weil hopes for his readers, then he has succeeded.

Wilson Marhin is one of the founding members of the medical student Complementary and Alternative Medicine club at the University of Toronto.

Being Open to Second Opinions

Sanjeev Luthra, B.A.Sc. (0T3)

Second Opinions: Stories of Intuition and Choice in a Changing World of Medicine

Jerome Groopman

Viking, 2000, 256 pp
hardcover, $38.50

For both patient and physician, it is often difficult to make medical decisions. The facts may not be clear, diagnosis not obvious, and prognosis uncertain. Nevertheless, important decisions cannot always be put off. Jerome Groopman, in *Second Opinions*, discusses the inherent challenges of medical decision-making and provides his experience as a helpful guide to both practitioners and patients.

Second Opinions consists of eight narratives, each dealing with a different aspect of medical decision-making. The common thread, as the title suggests, is the role of the second opinion. The first story illustrates this theme well. When Groopman and his wife took one of their sons to the hospital with an intussusception of the bowel (telescoping of one segment into another), they were unsatisfied with the service of the third-year resident who saw them. Although competent and well trained, he seemed aloof and overconfident. Groopman desperately sought another physician for advice, and through a distant contact found a second opinion. According to the new doctor, the bowel wall was close to rupturing; rapid intervention essentially saved the child's life.

Groopman reflects on that experience and highlights the importance of having the confidence to question one's physician and obtain a second opinion. He also asserts that doctors should be receptive to the advice of a colleague and should not hesitate in asking for help. Patient fear as well as physician arrogance can hamper communication. And communication is key to patient care and outcome.

Another important theme of the book is the role of intuition in medical decision-making. As Groopman points out, "a clinical compass is built not only from the doctor's medical knowledge but also from joining his intuition with that of his patient. This melding of minds occurs when the physician probes not only his patient's body but also the psychological and emotional needs."

Therefore, he argues that being receptive to the intuitive understanding that a patient has of his or her own condition is crucial in putting together a treatment plan that is both effective and satisfactory to the patient.

The doctor's intuition is also important. In a story about a physicist suffering from severe haematological dysfunction, a risky unmatched bone marrow transplant is suggested. Sensing the need for another opinion, the patient sought Dr. Groopman's counsel. Groopman based his advice on a 'dictum' learned in medical school: don't just do something – stand there. With no treatment at all, the patient surprisingly recovered. Sometimes you just have to go with your gut.

Other valuable aspects of *Second Opinions* are the discussions on medical genetics, the realities of working with health maintenance organisations (HMOs) in a privatized system, and the shortcomings of clinical trials. Each topic is discussed in the context of medical decision-making.

Not only does this book cover a wide variety of topics, it also provides a variety of perspectives. Dr. Groopman writes not only about his clinical experiences as a Harvard oncologist and Chief of Experimental Medicine at Beth Israel Deaconess Medical Centre but also about his own personal experiences as a patient, a parent to his sick child and close relative to his ailing grandfather. From this diversity of experience, the reader is exposed to the complexities of medical decision-making from different angles.

In conclusion, *Second Opinions* is an excellent book. Each story is presented clearly but with deep insight, perhaps not surprising for a physician of Groopman's stature. Most welcome, however, is the humility and humanism that suffuses each page. It is indeed warming to the heart to know that some medical leaders can embody such noble ideals.

UTMJ Crossword (answers on page 43)

Here at *UTMJ*, we are more than medicine - we're all about fun. As the editors wish your *UTMJ* experience is the most enjoyable, we have included some suggestions for:

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- Somewhat *UTMJ* content-oriented
- Somewhat not

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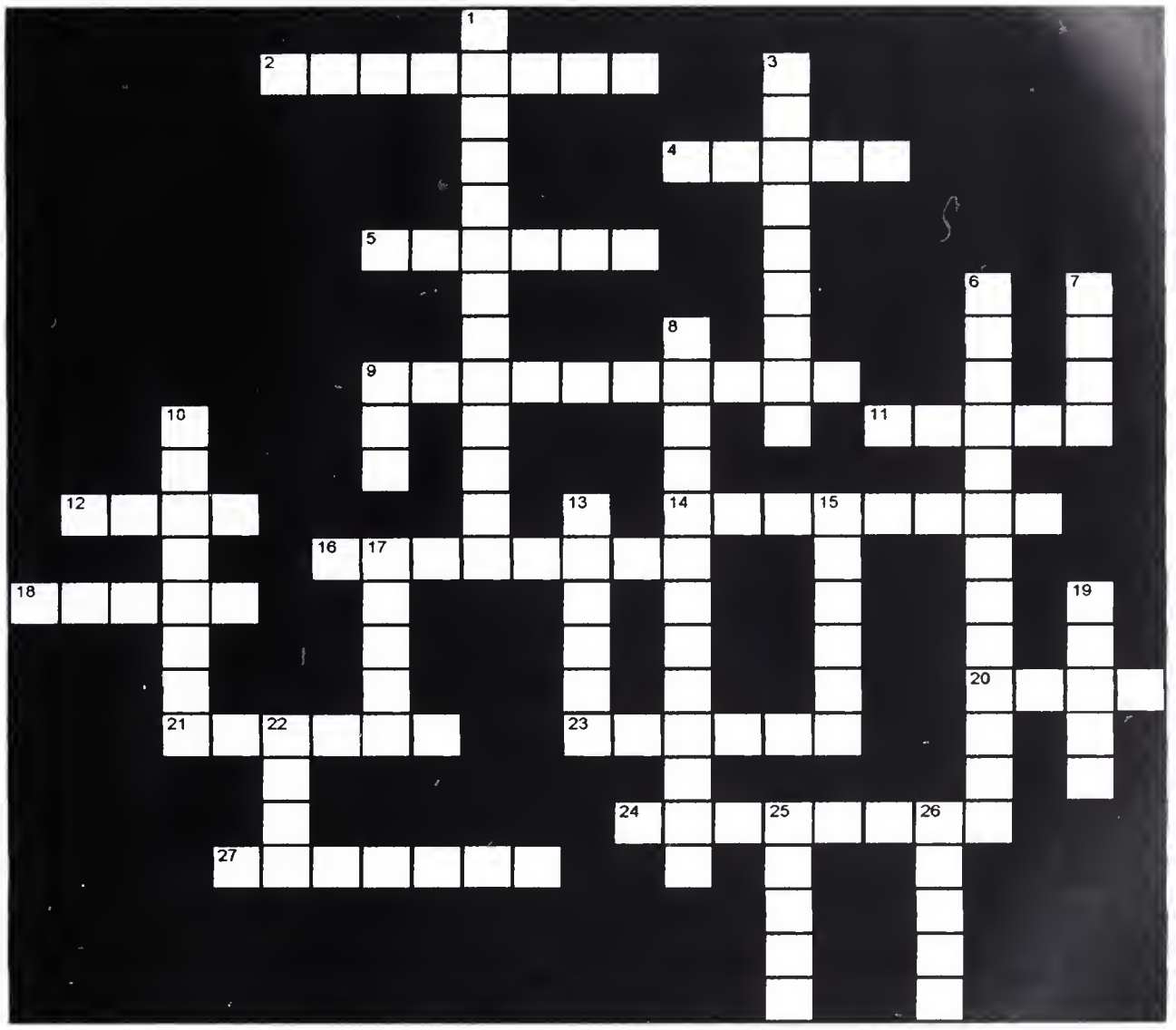

Across

2. Under the guise of DVT
4. Conrad's character moonlighting in Headhunter
5. Third molars
9. Dolly breed
11. Really large globulinemia
12. Largest human organ
14. ___ neuropathy
16. Digoxin
18. Cardinal signs of Compartment Syndrome
20. Singing with an editor
21. Well before Jerome's fifth opinion
23. Most lethal infectious disease
24. Often complicated
27. Toronto's contribution to chromosome 7

Down

1. Intimal thickening caused by the concentric proliferation of smooth muscle cells and the deposition of collagen
3. Andrew Lim and Warren Shi's emotional state
6. Polyneuropathic distribution
7. Number of Canadian boxing medals in Sydney
8. Everyone's favorite gait
9. Page
10. Oculomasticatory myorhythmia
13. One of these Afield
15. Always good to revisit or go "Back to"
17. Ethical donation requires autonomy
19. Grape juice; Discoverer of gas gangrene
22. A cold globulinemia
25. Set of drawers; Anatomical
26. 1970s sternal chest pain

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INSTRUCTIONS TO AUTHORS 2000-2001

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The paper should be submitted by an author, preferably the principal author, who should indicate in a covering letter:

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4. that all of the authors are aware of, and agree to, the content of the manuscript and that authorization has been given to use any information conveyed by either personal communication or release of unpublished experimental data;

5. three to six key words describing the paper, to assist in the selection of the reviewers.

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2. Kocsis JH, Davis JM, Katz MM, *et al.* (1985). Depressive behavioral and hyperactive adrenocortical function. *Am J Psychiatry*. 142: 1291-1298.

* Abbreviated journal titles should be used.

Articles **with more than 4 authors should include the first three authors followed by *et al.*

Article in a book or comparable publication

3. Smith MHD and Teele DW. (1995). Tuberculosis. *In: Infections diseases of the fetus and newborn infant, 4th ed.* Remington JS and Klein JO (eds). WB Saunders: Philadelphia, pp. 1074-1086.

4. Podolsky DK and KJ Isselbacher. (1998). Major complications of cirrhosis (ascites). *In: Harrison's Principals of Internal Medicine, 14th ed.* Fauci AS et al. (eds). McGraw-Hill, New York, pp. 210-214.

Books, theses, or comparable publication

5. Pressaco J and Yu H. (1996). *Pharmacological Treatment of Diseases.* Urban Angel Medical Books Inc: Toronto.

NEW: Web documents

6. Jacobson, J. W., Mulick, J. A., & Schwartz, A. A. (1995). A history of facilitated communication: Science, pseudoscience, and antiscience: Science working group on facilitated communication. American Psychologist, 50, 750–765. Retrieved January 25, 1996, from the World Wide Web: http://www.apa.org/journals/jacobson.html

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